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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

APRIL, 1926

ORIGINAL ARTICLES.

THE ADVANCEMENT OF EPIDEMIOLOGY THROUGH EXPERIMENT.*

By Simon Flexner, M.D.

NEW YORK CITY.

(From the Rockefeller Institute for Medical Research, New York.)

You have conferred a great honor upon me in inviting me to deliver the oration established in memory of the remarkable services of Doctor Weir Mitchell to science and to the public welfare. I know of no more fitting way to perpetuate the name and deeds of a man of science than by the creation . such an endowment as this. I wish that I felt better fitted to discharge the onerous duties of the occasion. But as one who was privileged to known Doctor Mitchell intimately and to come directly under the influence of his inspiration, I am very happy to be so circumstanced as to pay him tribute. Doctor Mitchell's deeds have added and will long continue to add luster to the city of Philadelphia; to the medical profession which he adorned; to the science of physiology from which, it is true, he withdrew for the wider field of neurology, but which nevertheless he never deserted nor ceased to love, and which either directly or indirectly he continued to enrich throughout his long, varied, and brilliant career; and finally to literature, to which he devoted those lighter hours of repose that the regularly recurring summer season brought into his busy life. Knowing Doctor Mitchell as I did, and his intense preoccupation with the nature of disease, I am con-

* The Weir Mitchell Oration, delivered at the College of Physicians, Philadelphia, December 16, 1925.

strained to believe that he would have been deeply interested in the theme of this evening's lecture. Since he never failed to follow the current of scientific progress, he would, I am confident, have welcomed the effort now being made to bring light and order into the vexed subject of epidemiology by seeking for it an experimental basis.

I. Historical Aspects.

Within the quarter century just closing, the United States together with many other countries has been passing through four considerable epidemics of disease—of cerebrospinal meningitis, poliomyelitis, influenza, and epidemic encephalitis. Each of these plagues has, either in turn or contemporaneously, claimed many victims, and excepting perhaps epidemic influenza, none of them has definitely run its course. The ravages still continue, and it is indeed not to be predicted when they are to cease and the conditions prevailing before their appearance be resumed.

There is small wonder, therefore, that the study of epidemiology should have come again to the front. A sorely harassed world is awaiting anxiously, as it were, a satisfactory answer to the question of the nature and the source of these pestilences of mankind. The question is of course not a new one and already not a few answers, none really adequate, have been made to it. But the state of the medical sciences at the present day would seem to give hope that knowledge not hitherto available may be secured from a fresh attempt at the solution of the biological problems involved.

We turn back to the father of medicine, as Hippocrates is admiringly and affectionately called, for the first recorded observations on the epidemic occurrences of disease. For it is true that the chapters on epidemics in his works consist of observations in which clinical course and states of the weather are considered in mutual relationship. Through this, then novel, way of viewing the onset and the symptoms of disease arose the doctrine of epidemic constitution, which has since played a major, if fitful part, in the history of epidemics. In developing this concept as applied either to climatic conditions of such marked type as to give a distinguishing character to a period of time, or to denote a fixed type of disease prevalent at a particular time, Hippocrates described actual occurrences which later writers translated into theories of the epidemic.[1]

The further development of the concept of epidemic constitution as a controlling or determining agency in bringing about the rise and fall of disease is attributed to Ballonius and to Sydenham.[2] The writings of the latter are more familiar to us and Sydenham's name is intimately associated in our minds with the doctrine. According to him, the potent influences are engendered through occult and inexplicable changes in the atmosphere, and are of a mysterious, so-called "skiey" nature, which determine the duration

and devastation of the prevailing disease. The constitutions differ in different years, depending upon hidden changes in the bowels of the earth, through which the atmosphere becomes contaminated and the bodies of men predisposed and made subject to this or that disease. A particular disease continues during the influence of a certain constitution, which after a cycle of a few years gives ground and makes way for another.[3]

All this may sound to us extremely mythical, and yet very recently the concept of constitution has been, indeed is being, reasserted in very respectable epidemiological quarters, in order to explain the epidemic happenings of the past twenty-five years. The question has been put whether in this period just such a cyclic succession of diseases and of constitutions, having a world-wide distribution, has not been taking place. Now it may be said, without any comment in advance, that it is not improbable that a doctrine so vital as that of epidemic constitution has shown itself to be, may after all, and in spite of certain vaguenesses and repellant features, still contain a morsel of precious truth, the detection and elucidation of which may be essential to a complete understanding of the nature of the processes—biological and physical—on which the occurrence of epidemics depends.

In Sydenham's day, the science of statistics was in its infancy in England and had not yet been born elsewhere.[4] With its rise and with the study of the written records of epidemics, there arose a new outlook in epidemiology which may be called the statistical-geographical, and which culminated, as it were, in the publication of Hirsch's great work between 1860 and 1864 on historical geographical pathology.[5] As presaging coming events which ushered in the bacteriological era, there appeared within this period two remarkable papers dealing with the innate nature of infectious disease, and postulating with a certainty and completeness not before attained the necessary or causal relation of microörganisms to the processes. I refer to Henle's epochal paper, "On miasms and contagia" of 1840 and the less celebrated one by Griesinger on "Typhus, typhoid, relapsing and malarial fevers," published between 1857 and 1864.[6]

Hard on the heels of Hirsch's monumental work came the epochal discoveries of Pasteur and Koch, their pupils and successors, which quickly transformed the entire scientific and practical outlook on the infectious diseases. The extraordinary discoveries in bacteriology, which now followed in almost bewildering rapidity of succession, raised strong hopes that the inner nature of the epidemic would be quickly revealed, a premature expectation which I need not tell this audience has not been entirely realized.

And yet the gains even within this field have not been small. I need merely to allude to the detection of the insect vectors of disease and the diminution brought about through the practical appli-

cation of this knowledge to malaria, which in many places has been thus and for the first time brought under control, and to yellow fever which has in the same manner been almost eradicated. Furthermore, through an adequately, scientifically based system of water purification, typhoid fever has been made to vanish from many strongholds, and the menace to the West of cholera has been reduced to impotence. The discovery of the power of protective inoculation has served still further to diminish the incidence of typhoid fever and allied diseases, and of diphtheria; and the detection of the healthy and other carriers of disease-producing germs has been rewarded by still further material reductions.

And yet we are so far from a complete understanding of the nature of infection in all its variegated and intricate forms as to be in certain instances, in epidemic influenza for example, impotent to affect its essentially undeviating course. The masters of bacteriology early perceived that infection is a process more subtle than the resultant of a mere bringing together of, on the one hand pathogenic microbe, and on the other susceptible host; and that about those factors played a series of adjusted biological reactions which ever since and increasingly it has become the task of the bacteriologist to disentangle. Somewhere within this field, once it is wholly won over to knowledge, lie the opportunity and the power to interfere with precision and certainty for the control of epidemic disease.

The discrepancy between the power of the microbe to strike and that of the host to defend led to the formulation of certain counter theories of the epidemic, in opposition to the purely bacteriological or etiological one coming into vogue. The counter theories still play a part in the history of epidemiology and, in one form or another, continue to be invoked, as has indeed just been done by Woltor in the case of the soil theory of von Pettenkofer, to account (I believe erroneously), in Russia especially, for postwar epidemics of typhus and other diseases which are, I think, more satisfactorily explained on the basis of famine, louse infestation, and like causes.[7] This notion put forward by von Pettenkofer postulates a certain prepared state, contamination or what not, of the soil as a forerunner and concomitant of epidemics, especially (although not exclusively) epidemics of typhoid fever and cholera. The theory has, with growing knowledge and improved communal sanitation, steadily lost ground and its revival seems inopportune and is not likely to bar real progress. On the other hand, Nägeli's diplastic theory, socalled, which assumes the coördination of two microbes—one, as we should now say, the specific, etiological incitant, visible, cultivatable, and so forth; and another, hypothetical and probably ultramicroscopic—has received an unexpected ally recently in Hamer, the British epidemiologist, who sees in the class of filter-passing organisms the second essential factor in the partnership.

Basing this view on de Schweinitz's discovery of the virus of hog cholera, Hamer constructs an imaginary pathology of influenza and other epidemic diseases, in which the filter-passer determines the kind of action which the specific, more obvious incitant, as for example the Pfeiffer bacillus, shall perform.[8]

We may discern in these revivals—epidemic constitution, contamination of the soil, coöperative or symbiotic action—the serious difficulties under which present-day epidemiologists are contending in the effort to bring light and order into the discussion of the nature and origin of the epidemic. The statistician too is groping more or less in the dark. The science of statistics has grown amazingly since Sydenham's day, and it is applied to an ever-widening circle of happenings, and often doubtless with remarkable results. As applied to epidemiology, we are enabled to envisage the perturbation of epidemic disease as never before: We follow now its imminence, onset, rise, and decline on a world-wide scale. By substituting, to use Greenwood's phrase, the herd for the individual, through depersonalization of disease phenomena, we have undoubtedly procured a body of data for analysis leading sometimes to useful or suggestive deduction. To mention one or two examples only, one thinks of Farr's generalization of the course of the epidemic in cattle plague in England, and Brownlee's hypothesis of a life cycle of the measles or other incitant, still awaiting discovery, which controls the appearance, disappearance, and reappearance of epidemic outbreaks of measles and possibly of other diseases.[9]

The bacteriological era in epidemiology is distinguished from its predecessors particularly by reason of the concept of strict specificity, or the operation of a particular microörganismal agent in producing a definite disease. In this important respect, the periods before and after Pasteur and Koch are widely separated. The isolation of tubercle, typhoid, and diphtheria bacilli, of trypanosomes and spirochetes, and a whole host of other microbes intimately associated with cases of infectious disease, and their clear biological distinction one from the other, led to the conviction of a particular parasite as the incitant of a particular disease. The strength of this belief in specificity is reflected in Koch's dictum that the parasite must always be found at the seat of disease and in the sick, but not in the healthy individual. In view of the frequency with which socalled "carriers" of pathogenic microbes are to be detected even among the healthy, this exclusive doctrine is no longer tenable, although it may not be affirmed that the newer discoveries in this field have severely shaken the concept of specificity. Rather it may be asserted that they have widened the outlook and led not only to the solution of riddles, otherwise unsolvable, in local outbreaks of infectious disease, but they have served to emphasize strongly the coördinate nature of infection and the interplay of forces as between microbe and host of previously unsuspected intricacy.

Up to this time the second partner, or host, had accorded him a subordinate, if not relatively an insignificant role. It became apparent, however, that not all individuals or groups equally exposed, equally responded to the exposure, and that with many epidemic diseases, sometimes racial, sometimes other characteristics seem to play determining parts. In regions in South America where yellow fever raged periodically, the dark or native population was observed to suffer less than the white immigrants, and the newly arrived among the latter oftener became victims than those already established or acclimated. Among animals, too, as in the notable nstance of insusceptibility of Algerian sheep to anthrax infection, such distinctions have existed. Whatever, therefore, might be thought regarding the activity of the microbic agents of disease, it was obvious that the host material is not an homogeneous one, and that previous and prolonged exposure to an epidemic disease does tend to decrease danger of attack.

The detection of carriers and especially the greater refinements of the bacteriological technic in revealing microbes potentially pathogenic as forming groups rather than as composed of sharply cut species, raised the questions whether they also do not show more or less heterogeneity. A vast literature on this subject has already come into existence and to it there are made almost daily additions, the sum of which has tended greatly to modify the older views of the fixity of bacterial strains. I desire to place emphasis on the point that in the brief description which follows, we are dealing not with the transformation of species, but rather with variation within given species, in which the ground or original type, phylogenetically speaking, remains undisturbed.

In 1902, de Vries announced mutation among the higher plants, and in 1906 M. Neisser and Massini described a mutating Bacillus coli which they termed "mutabilis." The twenty years intervening have witnessed the demarcation of large groups of related organisms, such as compose the dysentery and paratyphoid bacilli, and the pneumococci, streptococci, and meningococci—to mention only outstanding examples—in which distinctions are based on cultural, pathogenic, and immunological differences. Instability of type among certain bacterial groups and transition between types have often been asserted, but the conclusive evidences for such conversions have been slow in being brought forward. On the other hand, it is logical to suppose that with wide fluctuation among microbes, affecting even the quality of virulence, the possibility is to be reckoned with of particular variants (mutants?) of enhanced powers of infectivity, becoming dispersed and thus leading to epidemic outbreaks of disease.

The investigation of ordered variation or mutation among the bacteria was greatly advanced by de Kruif's observation of changes occurring in pure line strains of the bacillus of rabbit septicemia

(Bacterium lepisepticum) and of Arkwright's observations on Bacillus typhosus, paratyphosus, enteritidis, and dysenteriæ in 1921, through which the highly virulent *S* forms (growing in smooth colonies) become transformed into slightly virulent *R* forms (growing in rough colonies).* The two variants show immunological reactions more or less in common, but differ markedly in acid and saline agglutination points. The *S* strains tend in different degrees to give off *R* strains, while the latter doubtfully revert to *S*. In the case of the bacillus of rabbit septicemia, more closely studied perhaps than any other bacterium in this respect, the change from *R* to *S* has not been detected. The $S \rightarrow R$ mutation of this bacillus has been shown by Webster to depend on the oxygen tension of the culture, and to be favored by free oxygen and inhibited by oxygen absorbing substances (hemoglobin, etc.) in the medium. Reimer and Amoss, independently of each other, have recently promoted by special procedures the passage of pure-line strains of pneumococcus type I *S* into type I *R*, but have not been successful in bringing about the reverse transformation.[10]

Nor is this all. The pneumococcus and streptococcus groups of bacteria are doubtless closely related, and the distinction between them has long been regarded as indefinite. If, therefore, we are to accept recent perhaps inconclusive reports of Neufeld and of Morgenroth, we must admit transformations within groups tending still further to obscure the dividing lines. Moreover, Jordan has even reported an instance of reversion of a pure-line paratyphoid *R* into *S*. Not impossibly not one variant only, but a series of $S \rightarrow R$ variants is given off by certain bacteria, some slightly, some fundamentally altered in relation to the parent strain, according to which degree the $R \rightarrow S$ reversion may or may not be accomplished. The studies in this fascinating field are progressing rapidly, and it will be well to withhold judgment and prediction until we are possessed of far fuller data than are at present available. I commend to those intending to embark on these somewhat troubled and tedious investigations, the utilization of pure-line strains only derived from single bacteria as procured by the Barber or an equivalent technic, and the employment of as precise and rigid bacteriological and immunological methods as may be possible.[11]

To the epidemiologist this new knowledge and direction of research come with special force and significance. As his purpose is to account for the origin as well as for the movements of the epidemic, the life history of the microbes concerned becomes of high importance. Mutation or variation being now established as a not uncommon phenomenon, the question arises whether the change goes only in the direction of more to less, or may also proceed in the direction

* De Kruif used the letters *D* (diffusely growing in broth) and *G* (granular growing) to designate the two forms. But Arkwright's designations *S* and *R* have now been generally adopted.

of less to greater virulence. *The fact should, therefore, not be lost sight of that up to now the changes observed have been of the nature of a degradation and not of an exaltation of pathogenicity*, and while it cannot of course be denied that the reverse process is capable of taking place, we must admit the lack of convincing evidence of its significant occurrence.

At this point I shall digress in order to present to you an instance of rise in power of the virus of poliomyelitis which came to the attention of Dr. Harold L. Amoss and myself. Unfortunately, the conditions under which the rise, fall, and second rise in the activity of the virus took place were not such as to permit any clear insight into the precise factors involved, as for example, whether merely one alone or several virus strains collectively were involved. And yet the incident is not without suggestive value. But the circumstances under which it was noted are so onerous that the observation is not likely soon to be repeated.

Beginning almost with the appearance of epidemic poliomyelitis in the United States in 1907, experimental studies were carried out at the Rockefeller Institute. A strain of human virus was implanted in rhesus monkeys. It was at first of low virulence, but a few passages enhanced its activity for the animals, and soon maximal virulence was attained and maintained by systematic inoculations for a term of three years. Then for wholly unknown reasons, diminution set in and the virus returned approximately to the low level of the original human material. Samples of the nervous tissues of infected monkeys had been regularly preserved in glycerol at +4° C., and these samples were retested from time to time to determine activity. About six years after the virus had diminished in infectivity, a rise in power was noted, and a second high level was attained about equalling the first. The enhanced virus has remained at that level during the past five years. Briefly, this specimen of of virus passed through several distinct phases of activity: low, high, low, and again high, the last stage while specimens of nervous tissue were preserved in glycerol for several years without being subjected to animal passage.[12]

Certain epidemiologists, and notably Gotschlich, emphasizing the phylogenetic ascent of parasites from saprophytic bacteria, cite certain occurrences as indicating the transformation in nature of nonpathogenic into pathogenic organisms.[13] Such a supposed instance is that of Uhlenhuth and Zuelzer who, by employing animal passages, believed that they accomplished the conversion of a saprophytic water spiral into a pathogenic variety.[14] However, Neufeld, an authority who favors the general point of view expressed, does not accept the interpretation given of this particular example.[15] Gotschlich, on the other hand, sees in the reappearance, after long cessation, of cholera in 1817 and of plague in 1894 in India, the operation of natural causes transforming the corresponding sapro-

phytic into parasitic incitants of these diseases, a conclusion which with present knowledge will be acceptable to few bacteriologists. Neufeld among others urges that pandemics of influenza arise, not through successive distribution from one place to others of the highly virulent microbic incitant, but by reason of regional transformations of bacterial strains of low infectivity into strains of maximal virulence. That selected, more highly infective strains of pathogenic bacteria may be secured by animal passages is something pointed out by Pasteur and accomplished every day in the laboratory. But no experienced bacteriologist sees in this device the production of new or enhanced bacterial variants or species. The Germans, as do we, distinguish between mere separation or selection (*Auslese*) and modification (*Umstimmung*) by mutation or some other process of variation. Even as regards epidemic influenza, one cannot accept ûnqualifiedly the "local,"as it may be termed, passage from low to high virulence of a microörganism, as accounting for the pandemics of that disease, seeing that outbursts follow lines of human travel, proceed in a geographical and chronological order, sweep past inaccessible communities, and show in general that characteristic to which the name "posting" has long since been applied.

Conscious of the inadequacy of the evidence adduced for the belief in microbic variation or mutation as accounting for the rise of epidemics, the protagonists of this view, as instanced by Neufeld, hold that support for it is to be sought in the appearance of new diseases. If it is admitted that the parasitic organisms have evolved from saprophytic ancestors, then at some period in history, the specific infections which have endured, must have emerged and presented themselves for the first time. It is, of course, entirely possible that none of our laboratory procedures suffices to initiate the transmutations involved. We should, therefore, be on the lookout for the occurrence of new types of infectious disease, incited by microörganisms not previously known. No one would, of course, wish to deflect this quest, or deny the possibility of a successful issue. A pertinent question just now would be whether epidemic encephalitis may be regarded as a "new" disease. We are unfortunately in the weak position of not having discovered the incitant; and yet it is true that present-day internists and pathologists have had no previous experience of an epidemic disease of the nervous system corresponding to the multiform encephalitis. Even assuming that the incitant were actually isolated and proved wholly distinct from known pathogenic organisms, would the case for the "new" disease and the transformed parasite be proved? It may, I think, be doubted, in spite even of the incontestable fact that no such nervous disease had until recently come to the attention of physicians, and notwithstanding chronological relations to the recent pandemic of influenza, no corresponding epidemic disease

attended the influenza outbursts of 1889 to 1892. Yet when the older records of epidemics, of which some certainly were and others might have been influenza, are searched as has been done so laboriously and interestingly by Crookshank, there are revealed associated occurrences of nervous or paralytic diseases to which one might hesitate to deny similarity with or relation to the epidemic encephalitis of the present time.[16] As one holding the view that epidemic influenza and epidemic encephalitis are distinct entities, I wish nevertheless to put these facts before you. It cannot, moreover, be entirely without corroborative weight that although epidemic influenza ceased to prevail in this country in 1922–1923, yet epidemic encephalitis still marches on. The two diseases are surely not united specifically: whether they are engendered within a particular constitutional cycle, as Crookshank's argument implies, may be regarded as a hypothetical question which perhaps the experimentalist may ultimately be able to solve.

Let us, therefore, for the time being rest the case from the standpoint of human epidemic disease just here. If I have hurried you along rather breathlessly in epitomizing the present state of epidemiology, as ordinarily conceived, it is because I wish to lay before you a possible new mode of approach to some of its problems which, up to now, has been perhaps less invoked than it deserves. I refer to the study in relation to causes and effects of the epidemics occurring among animals to which we have ready access. Now all animals, even the most lowly, and plants of course, suffer from epidemic diseases. There is good reason for believing that in essential respects the happenings are comparable in all. Just the other day I read an account of an epidemic which swept through and destroyed most of that devastating pest, the Mexican bean beetle—but not all—in one of the southern states. This imperfection of extermination is a characteristic of all epidemics, even the severest of man and animals. There is always a remnant of saving grace in the worst outbreaks.

The second or experimental part of this lecture* deals with epidemics among mice and rabbits, the study of which has occupied us at the Rockefeller Institute for five years or more. I am led to report these studies in detail because I believe that they help us to comprehend better the events occurring in human epidemics Doubtless in time epidemics among still other, perhaps still smaller animals, which can be numerously assembled, will come to be investigated. How far down the living scale we must go before we reach the limit of epidemics is not yet determined. Many of you know that d'Herelle, who has conducted remarkable investigations of the dissolving effects on bacteria of his socalled phage, conceives

* To appear in the next number.

the active agent as a living virus—a kind of still smaller parasite within the bacteria affected. Although this happens not to be the generally entertained view of the undoubted phenomenon of bacterial autosolution, yet the event serves to recall the satiric lines of Swift, which I venture to quote in this connection:

> So, naturalists observe, a flea
> Has smaller fleas that on him prey;
> And these have smaller still to bite 'em;
> And so proceed *ad infinitum*.

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THE MODE OF DEATH IN VARIOUS TYPES OF HEART DISEASE.

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In order to determine the mode of death when patients died from heart disease and to attempt an analysis of the contributory factors, a consecutive group of 330 cases was selected. The cases chosen were those in which death was directly attributable to the cardiac disease.

In the analysis of clinical cases of any type it must be conceded that variations occur in the degree of severity of similar types of disease and, therefore, that similar material in various medical centers will possess certain differences. This point gains emphasis in the comparison, for instance, of a group of cases of heart disease encountered in private practice and a similar group selected from a coroner's record.

Most of the patients with heart disease coming to the Mayo Clinic are ambulatory, although many of them are afflicted with advanced and serious disease. Many of them also have come from great distances and the stress and strain of arduous journeys render their condition more critical. These factors unquestionably influence the results of this study.

Arteriosclerotic Cardiac Disease.[1] There were eighty-two deaths in cases in which the diagnosis of arteriosclerotic cardiac disease was made and in 82 per cent of these cases necropsy was performed and the diagnosis confirmed. Fifty-nine patients were males and twenty-three were females, the greatest incidence occurring in the sixth and seventh decades of life in which 26 and 34 cases, respectively, occurred. The youngest patient was a man, aged thirty-three years, who died from gradual heart failure; necropsy revealed extensive coronary sclerosis. Forty patients (49 per cent) died suddenly, while forty-two (51 per cent) died from gradual heart failure. Of the twenty-three patients who were known to have had angina pectoris, nineteen died suddenly.

Nine patients had embolic phenomena and undoubtedly embolism was an important factor contributing to death. Four patients had multiple pulmonary infarcts as a result of mural thrombosis of the right ventricle. In one instance the pulmonary artery was occluded by a thrombus arising in the right heart, in one a thrombus in the right femoral vein produced multiple pulmonary infarcts. There were 2 cases of cerebral embolism, 1 resulting from a mural

[1] This group does not include cases of myocardial infarction, which will be discussed separately.

thrombus of the left auricle and the other from the left ventricle. In another case mural thrombi in both ventricles resulted in infarcts of the lungs, spleen and left kidney. Auricular fibrillation occurred in only 6 cases and in only one instance was death sudden. There were 3 cases of complete heart block, the patients all dying suddenly with Stokes-Adams phenomena. Only 1 case of auricular flutter was recorded, the patient dying suddenly during a rapid paroxysm when the ventricular rate attained that of the auricles.

Myocardial Infarction. The diagnosis of infarction of the myocardium occurred in 35 cases. A marked predominance occurred among males, in whom the incidence was 30, while only 5 cases occurred among females. Necropsy was performed in 97 per cent of the cases. Nineteen and 10 cases, respectively, occurred in the sixth and seventh decades. It is interesting to note that the youngest patient was a woman aged only twenty-eight years. Death occurred suddenly and necropsy showed extreme sclerosis of both main coronary vessels with chronic infarction of both ventricles. There were no findings to indicate a syphilitic process. Acute infarction occurred in 15 cases while the process was either ancient or gradual in 20 cases. Death occurred suddenly in 25 cases (71 per cent) and resulted from gradual heart failure in 10 (29 per cent). Sixteen patients were known to have had angina pectoris, nine died suddenly, and seven died from gradual heart failure.

In the cases in which necropsy was performed the left coronary artery was occluded in 29, the right in 2, both the right and the left in 2, and in 1 case the infarction was situated in the interventricular septum. Cardiac aneurysm involved the left ventricle in 4 cases and in 1 of these rupture had occurred with hemorrhage into the pericardial sac.

Embolic processes occurred in 4 cases. Mural thrombosis of the left ventricle in 2 cases resulted in emboli to the superior mesenteric artery with infarction of the small intestine. In 1 case a mural thrombus of the left ventricle caused cerebral embolism, and in 1 case multiple pulmonary infarcts occurred from mural thrombosis of the right auricle. Auricular fibrillation was known to be present in only 2 cases.

Hypertensive Cardiac Disease. In 39 cases of hypertensive cardiac disease death was attributed directly to the heart. Necropsy was performed in 87 per cent of the cases. Twenty-eight patients were males and eleven were females. The greatest incidence occurred in the fifth, sixth and seventh decades, in which eleven, seven and fifteen deaths occurred, respectively. Twelve patients (31 per cent) died suddenly, twenty-seven (69 per cent) died from gradual cardiac failure. Embolic phenomena occurred in only 4 cases, in 2 of which thrombi from the right heart occluded the pulmonary artery while in the other 2 mural thrombi from the right auricle produced multiple pulmonary infarcts. Eight cases of auricular fibrillation were recorded.

Cardiac Hypertrophy Associated with Obesity. In 2 cases of marked cardiac enlargement with fatty myocardial changes, no basis for the heart findings was demonstrable other than obesity. There were no findings or history of hypertension, no coronary changes, and no evidence of adhesive pericarditis or valvular disease. The patients were both males, aged thirty-three and fifty-four years, respectively. Both died suddenly; both had pulmonary infarcts.

Acute Myocarditis. One patient, a man, aged thirty-four years, died suddenly and necropsy revealed acute myocarditis. There was no evidence of endocardial disease.

Cardiac Failure from Mechanical Causes. In 2 cases death directly attributable to cardiac failure occurred from mechanical causes. The first patient was a male, aged nineteen years, who died suddenly. Marked dilatation of the right auricle and ventricle had been caused by pressure from an extreme deformity following tuberculous spondylitis in the upper cervical region. The other patient was a man, aged thirty-three years, who died from gradual cardiac failure. Extreme kyphoscoliosis was present, the displaced vertebral column having caused partial obstruction of the pulmonary artery which resulted in marked hypertrophy and dilatation of the right ventricle.

Chronic Endocardial Valvular Disease. There were 91 cases in which the diagnosis of chronic endocardial valvular disease was made and necropsy was performed in 76 per cent of the cases and the diagnosis confirmed. The sex incidence was practically equal, there being forty-nine males and forty-two females. Two deaths occurred in the first decade, ten in the second, thirteen in the third, twenty-two in the fourth, seventeen in the fifth, sixteen in the sixth, ten in the seventh and one in the eighth. Twenty-three patients (25 per cent) died suddenly, and sixty-eight (75 per cent) died from gradual cardiac failure.

Mitral Stenosis. Mitral stenosis as the predominant lesion occurred in 59 cases (65 per cent). Twenty-six patients were males and thirty-three were females. Sixteen patients (27 per cent) died suddenly, and forty-three (73 per cent) died from gradual cardiac failure. The aortic valves were also affected in eight patients, the tricuspid in three, the aortic and tricuspid valves in one, and the tricuspid and pulmonic valves in one. The mitral valve alone showed evidence of disease in forty-six patients.

Embolic phenomena occurred in 14 cases. In 9 cases mural thrombosis of the right auricle resulted in multiple pulmonary infarcts. Cerebral emboli in 3 cases resulted from mural thrombosis of the left auricle and in 1 case left auricular thrombosis produced a right femoral embolism. In another case an embolus from a thrombus of the left auricle entered the coronary circulation with resulting fatal myocardial infarction. Auricular fibrillation was present in 8 of these cases. Auricular fibrillation was known to

be present in 21 cases of mitral stenosis. Auricular flutter occurred in 1 case in which death was sudden.

Aortic Insufficiency (nonsyphilitic). In 21 cases (23 per cent) nonsyphilitic aortic insufficiency was the dominant abnormality. Sixteen patients were males and five were females. Two patients (10 per cent) died suddenly, and nineteen (90 per cent) died from gradual cardiac failure.

The mitral valve was also affected in 11 cases, all the valves in 1 case, the mitral and the tricuspid valves in 1, and the tricuspid valve in 1. The aortic valve alone showed evidence of being affected in 7 cases. Embolic phenomena occurred in only 3 cases; infarcts were present in the spleen and right kidney in 1 case; in the lungs, kidneys and spleen in 1 case, and in the spleen alone in the third case. Auricular fibrillation occurred in 3 cases and in none of these did embolic phenomena occur.

Aortic Stenosis (nonsyphilitis). Aortic stenosis was diagnosed in 11 cases (12 per cent). Seven patients were males and four were females. Five patients (45 per cent) died suddenly and six (55 per cent) from gradual cardiac failure. In 4 cases the mitral valve was also affected while in 7 cases the pathologic process was not found to extend beyond the aortic valve. There were embolic phenomena in 4 cases. Infarction of the spleen occurred in 1 case, infarcts of the spleen and brain in 1 case, and multiple pulmonary infarcts from mural thrombosis of the right auricle in 2 cases. Only one patient was known to have had auricular fibrillation. One had complete heart block and died suddenly during a Stokes-Adams seizure.

Bacterial Endocarditis. *Acute Bacterial Endocarditis.* Acute bacterial endocarditis was found in 3 cases. Two patients were males and one was a female. The patients were aged thirty-one, thirty-two and forty-nine years, respectively. None died suddenly. In 2 cases Staphylococcus aureus was the infecting organism, while the pneumococcus was recovered in the third. The aortic valve alone was involved in both cases due to Staphylococcus aureus, and the tricuspid valve alone in the case due to the pneumococcus. In 1 case pulmonary and in another splenic infarction occurred.

Subacute Bacterial Endocarditis. Subacute bacterial endocarditis (anhemolytic streptococcus) was diagnosed in 26 cases. Necropsy was performed in 88 per cent and the diagnosis confirmed. Nineteen of the patients were males and seven were females. One was in the second decade, nine were in the third and the fourth decades, three were in the fifth and four in the sixth decade. None died suddenly. The mitral valve alone was found affected in 12 cases, the mitral and aortic in 8, the aortic valve alone in 4, the pulmonic valve in 1 case, and the tricuspid valve in 1. Embolic phenomena occurred in 13 cases. In 7 cases there were multiple splenic infarcts, in 3 infarcts in the spleen and kidney, and in 1 case multiple

infarcts of the spleen, kidney and intestines. In 1 case single cerebral embolism was present and in 1 mycotic aneurysm of the left middle temporal artery, as well as mycotic aneurysm of the pancreatic artery and infarcts in the spleen and kidneys. There was no instance of auricular fibrillation.

Pericarditis. *Chronic Adhesive Pericarditis.* There were 12 cases in which chronic adhesive pericarditis was found; necropsy was performed in all cases. Eleven patients were males and one was a female. One was in the second decade, three were in the third, four in the fourth, three in the fifth, and one in the sixth. Only two patients died suddenly. Embolic phenomena occurred in only 1 case in which multiple pulmonary infarcts were found. In 5 cases there was associated endocardial valvular disease. Auricular fibrillation was known to be present in 1 case only.

Acute Suppurative Pericarditis. In 3 cases, acute suppurative pericarditis was the cause of death. Two patients were females and one was a male, aged one, two, and forty years respectively. Necropsy was performed in all the cases. There were no sudden deaths.

Tuberculous Pericarditis. One patient, a man, aged thirty-six years, died from tuberculous pericarditis. There had been a recurrent chronic massive effusion, and at one time 1500 cc. of fluid was aspirated. Death occurred gradually, and necropsy revealed extensive thrombosis of the veins of the thorax and neck.

Carcinoma of the Pericardium. A woman, aged forty-one years, died from massive carcinoma of the pericardium secondary to a small focus in a bronchial gland. The clinical picture was characterized by recurrent hemorrhagic effusion. Death occurred after a protracted illness.

Cardiovascular Syphilis. *Thoracic Aneurysm.* Ten patients died from thoracic aneurysm. Necropsy was performed in all cases. Nine patients were males and one was a female. Five were in the sixth decade of life. Eight patients died suddenly, in all instances from rupture of the aneurysm. The rupture was into the trachea in 2 cases, into the esophagus in 2, into the pericardial sac in 2, and into the left pleural cavity in 1 case. The aneurysm involved the arch of the aorta in 7 cases, the ascending aorta in 2, and the descending aorta in 7. They were of the fusiform type in 5 cases, the saccular type in 3, fusiform and saccular in 1 case, and the dissecting type in 1.

Aortitis. Eighteen patients died from syphilitic aortitis, and necropsy was performed in 94 per cent. Sixteen of the patients were males and two were females. The greatest incidence occurred in the fifth decade in which 10 cases were recorded. Eight patients died suddenly. Three of these had marked stenosis of the coronary orifices. One patient had thrombosis of the mesenteric artery. None had auricular fibrillation.

Congenital Cardiac Disease. Four patients had congenital heart disease. Two patients were males and two were females, aged three days, four days, twenty-three months, and twenty-six years respectively. Necropsy was performed in all cases. The patient aged three days died suddenly and at necropsy congenital coarctation of the aorta associated with patency of the ductus arteriosus (Botalli) was found. The patient aged four days died suddenly and patency of the foramen ovale was found at necropsy. The patient aged twenty-three months, who had stenosis of the isthmus of the aorta associated with partial defect of the interventricular septum and patency of the ductus arteriosus (Botalli), died from gradual cardiac failure. The patient aged twenty-six years died from gradual cardiac failure due to congenital atresia of the mitral and tricuspid rings. Infarction of the lungs, kidneys and spleen had occurred.

Summary. In a review of 330 cases in which death occurred as the direct result of cardiac disease, clinically or pathologically determined, the types were as follows: (1) Arteriosclerotic cardiac disease, 25 per cent; (2) myocardial infarction, 11 per cent; (3) hypertensive cardiac disease, 12 per cent; (4) cardiac hypertrophy associated with obesity, 0.6 per cent; (5) acute myocarditis, 0.3 per cent; (6) cardiac failure from mechanical causes, 0.6 per cent; (7) chronic endocardial valvular disease, 28 per cent; (8) bacterial endocarditis, 9 per cent;(9) pericardial disease, 5 per cent; (10) cardiovascular syphilis, 8 per cent; (11) congenital cardiac disease, 1 per cent. Sudden death occurred in 125 cases (38 per cent), while death from gradual cardiac failure occurred in 205 cases (62 per cent). Embolic phenomena occurred in 58 cases. Necropsy was performed in 85 per cent of the cases reported.

INTERMITTENT AURICULAR VENTRICULAR BLOCK.

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and

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That the presence of intermittent heart block is not necessarily of grave immediate prognosis is shown in the reports of several writers. Russell-Wells and Wiltshire[1] had a patient with this condition under observation for twelve years, and Bullrich[2] reported in 1924 that the patient whom he believed had been cured of heart block in 1921, again had block. This would suggest that the pathologic process responsible for the transient abnormal rhythm might

have been, in itself, of relatively minor importance as regards life. The causes of the interference with conductivity vary widely. Krumbhaar[3] reported a series of cases showing transient block due to an acute infection in one instance, to the effect of digitalis in another, and in another case to delayed conduction in the right bundle branch. Gager and Pardee[4] record a case in which the heart passed from complete block through 2 to 1 block into a normal rhythm, later returning to a complete block. This patient repeatedly went into periods of ventricular standstill lasting from six to nineteen seconds, during which the patient became unconscious, often having convulsions before the resumption of ventricular action. Carter and Dieuaide[5] found in the literature only 8 cases recorded similar to their own, in which there were attacks of syncope and complete block, alternating with a normal rhythm between attacks. It is worthy of note that in all of these 9 patients, the *a-c* interval, or the *P–R* interval, was from 0.17 to 0.20 seconds both before and after the attacks of block.

Variations of a paroxysmal type between the normal heart rhythm and any of the abnormal rhythms are not recognized very frequently, although such conditions must be relatively common. In part the difficulty in discovering fugitive abnormal rhythms comes from the impossibility of examining a particular patient for twenty-four hours daily; in part from the labor and expense involved in making long-continued graphic records of any sort and the natural improbability of the expected change of rhythm appearing at the particular time during which the patient's heart action is being recorded. It would appear that polygraph tracings or electrocardiograms showing the transition from a period of block to a period of normal rhythm are rare.

The remarkable point to be seen in the record of this change in ventricular rate in the case here reported is the quietness of the transition, the absence of evident change in mechanism; there is nothing to show why the auricular impulses were previously blocked, nor why conductivity has increased. The heart merely goes from one rhythm to the other, without preliminary, and with only a slight change in the *a-c* interval; the *a-c* conduction time for the first of the normal ventricular beats to come through is slightly greater than when the ventricle was beating at half the rate. From that point on, as one might expect, the conduction rate continues to be slightly slower than during the period of block, due to the increased work put upon the conducting paths, but still practically within the outer limits of normal conductivity, (0.25 second).* This last fact, it seems to us, is the essential in the possible occurrence

* Mackenzie considers the usual duration of the *a-c* interval in normal hearts as 0.2 seconds. (Mackenzie, James: Diseases of the Heart, 1918, p. 262.) Lewis gives the normal *a-c* interval as between 0.1 and 0.2 seconds. (Lewis, Thomas: Mechanism and Graphic Registration of the Heart Beat, 1920, p. 29.)

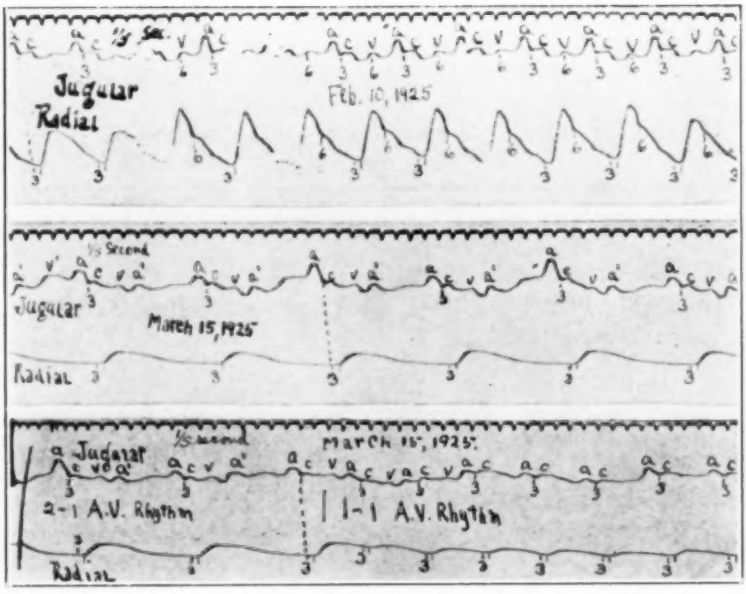

FIG. 1.—Polygrams. Upper tracing shows normal rhythm; middle tracing, 2 to 1 block; lower tracing shows the transition from a 2 to 1 rhythm to a normal rhythm.

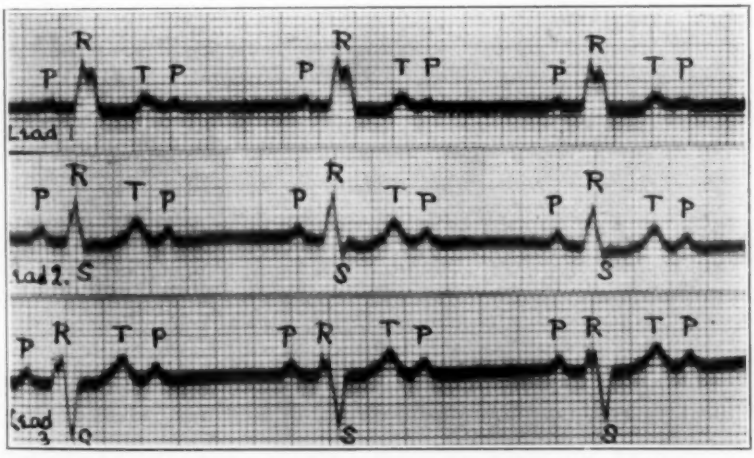

FIG. 2.—Electrocardiogram made March 17, 1925. Shows better conduction in the right bundle branch than was the case on February 4. All of the electrocardiograms show a *P–R* interval that is within normal limits.

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of a spontaneous paroxysmal block While here the heart was seriously damaged, as evidenced in several electrocardiograms, a P–R interval of 0.2 second is not evidence of a sufficiently high grade of block to prevent return to a normal rhythm.* This is also brought out in the review of 9 cases of transient block by Carter and Dieuaide previously noted, for in no one of the cases was the conduction time greater than normal, either before or after the period of block. These authors also offer an hypothesis for the occurrence of the change in rhythm, that is both simple and logical. According to their view, in these hearts the bundle of His contains a few intact fibers, just equal to the work of conducting impulses normally under favorable conditions, but incapable of transmitting the stimuli whenever stresses of any sort occur. In our case, we had no evidence of complete block at any time, nor did the patient have syncopal attacks while under observation, but since he had had six attacks of unconsciousness during the six months previous to his admission to hospital, he may have had a higher grade of block on those occasions. It seems probable that the block in the case here reported was due to right-bundle-branch defect. One most interesting feature of the case was that the patient felt very much better when his heart was in a state of block, than when normal rhythm was present.

Case Report. A. V., a white widower, aged seventy-six years, a fisherman, was admitted to the Boston City Hospital on February 3, 1925. His wife had died at the age of fifty-four years, of cancer; his three children were living and well. Until a year ago, the patient had always been in good health; lately, he had been forced to limit his activities. He began to have some breathlessness on exertion. During the six months before admission, he had had six fainting spells; at one of them he fell unconscious against a hot stove and burned his arm. Two days before admission he pulled a tooth, which procedure was followed by profuse bleeding. He has no knowledge of having been treated with digitalis.

Physical examination showed a very weak old man, apparently somewhat dazed, lying quietly in bed. His pupils were slightly irregular, markedly unequal, the left one being dilated; both reacted well to light and distance. He showed no bleeding from the gums. The lungs were negative. The heart was slightly enlarged to the left, apex impulse being felt 11.5 cm. to the left of the midsternal line; left border of dullness corresponded; supracardiac dullness was 5.5 cm. in width. The sounds were of poor quality; only one sound was heard, probably the first, and it was valvular in quality. The rhythm was regular, at a rate of 40 per minute. Neither the aortic nor the pulmonic second sound was heard, and no murmurs

* Lewis found that in healthy young men the P–R interval might reach as great a duration as 0.21 seconds. (Loc. cit., p. 51.)

were made out. The radial arteries were markedly sclerosed and tortuous, and the pulse rate corresponded to that of the apex. The liver was not felt; there was no ankle edema; knee jerks were slightly hyperactive. The urine was normal; blood pressure low 130/90; Wassermann negative.

An electrocardiogram taken February 4, showed partial *A–V* block, 2 to 1 rhythm. Rate of auricle = 90; of ventricle = 45. *P–R* interval = 0.20 second. $P_2 = 0.2$ millivolt. Intraventricular block, right branch, *Q R S* = 0.14 to 0.16 second and notched. His pulse gradually increased in rate, still keeping quite regular, until on February 21, it reached its maximum of 72 per minute. He was now apparently out of block, as confirmed by another electrocardiogram, which showed normal rhythm. On February 22, he again went into block, his pulse going to 40, remaining there until March 8, when he was given large doses of caffein sodiobenzoate (gr. xxi) subcutaneously every four hours during a twelve-hour period.

Following this rather radical treatment, the patient's pulse varied tremendously. At times the rate would be normal, at times very slow. During the slow periods the patient felt fine; during the rapid ones, he felt worse. While in the hospital he received no digitalis.

On March 15, a polygraph tracing was taken (Fig. 1). After a long strip showing the 2 to 1 rhythm, normal rhythm suddenly returned, showing no very definite evidence as to a change in mechanism, except that the *a c* interval increased from about 0.20 to 0.25 second. This may be taken as being the high normal limit for conduction time. The pulse rate during the period of block was 36; after return to normal rhythm, 70. A tracing of February 10, shows normal rhythm with an *a-c* interval of 0.2 second and rate of 66.

An electrocardiogram on March 17 (Fig. 2) shows 2 to 1 block, with rates of 84 and 42; *Q–R–S* interval 0.12 to 0.14 second; otherwise like previous report.

The patient gradually improved symptomatically, and was discharged as improved, on March 23, 1925.

The patient whose case is here recorded was visited on January 23, 1926. He had had no attacks of syncope since leaving the hospital last March. He is able to get about the house, but has been out to walk only three times, as he gets short of breath very quickly and has to sit down to rest. His only complaints are pain in the back of his neck and in his left hand. A polygram taken at this time shows a 2 to 1 block, with an auricular rate of 64 and a ventricular rate of 32. The *a-c* interval varies from 0.2 seconds to 0.5 seconds, averaging about 0.35 seconds. There is no essential change in the physical examination, and the only evidence of decompensation is the occurrence of dyspnea on slight exertion.

Conclusions. 1. A case of transient 2 to 1 auricular ventricular block, apparently due to right bundle branch defect, is reported.

2. The transition from a period of 2 to 1 block to a period of normal rhythm, as recorded by the polygraph, is perfectly smooth and unbroken, giving no evidence of a change in mechanism, nor any definite explanation for the presence of the abnormal rhythm.

3. It is believed that alternation between normal conduction and auricular ventricular block, is possible only when the *P–R* interval (*a-c* interval) is practically within normal limits; that is when the delay in conduction between auricle and ventricle is not in itself sufficient to account for the blocking of the auricular impulse.

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CEREBRAL MANIFESTATIONS OF PAROXYSMAL TACHYCARDIA.

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Although the literature on paroxysmal tachycardia is voluminous, there have been few reports in which cerebral symptoms were associated. Savini, in 1912, spoke of a syncopal form of paroxysmal tachycardia, and Esmein and Donzelot, accepting this as a special type, reported a similar case and discussed the mechanism of its production. In speaking of symptoms of cerebral anemia, Hirschfelder asserted that weakness, vertigo, nervousness, insomnia, and even syncope, may occur. He cited 1 of his own cases in which syncopal attacks had led several prominent physicians to diagnose Adams-Stokes syndrome, but further observation showed that the seizures were attended by tachycardia and not by bradycardia.

In a previous study of paroxysmal tachycardia,[5] verified by electrocardiographic tracings, it was pointed out that the prognosis in cases of paroxysmal tachycardia without signs of organic heart disease is good, and that attacks are compatible with long life, but that if attacks occur in conjunction with organic heart disease the prognosis is determined by the type and degree of the underlying cardiac damage. The frequency of cerebral mani-

festations was striking, and therefore this group seemed worthy of a special report.

Fifteen cases were studied; 10 of the patients were males and 5 were females. Their average age was forty-one years; the oldest was sixty-two, and the youngest twenty-four. In 6 cases there was a history of attacks of tonsillitis, and in 9 a history of influenza. Other antecedent infections included typhoid fever in 2 cases, rheumatic fever in 2, syphilis in 2 and pneumonia in 1 case.

Examination showed definite evidence of tonsillar infection in 6 cases and dental infection in 5. Tonsillectomy was performed in 4 cases; in 1 of these the paroxysms ceased for eighteen months and then recurred; there were no further attacks after tonsillectomy in 1 case, and the paroxysms were not influenced in 2 cases. In 11 cases no associated disease was found. In 2 cases syphilis was present, and in 1 of these diabetes mellitus also. Marked secondary anemia of undetermined origin was found in 1 case.

No organic heart disease was demonstrable in 10 cases. In 2 cases there was chronic mitral endocarditis with stenosis, and in 1 of these associated mitral insufficiency. Syphilitic aortitis was present in 1 case. A serious degree of myocardial degeneration with auricular flutter was found in 1 case and angina pectoris in another. In 4 cases in which there was definite organic heart disease the attacks were no more severe than in the group of cases in which the hearts were normal. In 1 case in which there was mitral stenosis and insufficiency a paroxysm of tachycardia was complicated by an alarming attack of pulmonary edema and coma of three days' duration.

The blood-pressure readings between attacks varied little from normal. The average systolic pressure was 129, the highest measuring 162 and the lowest 108. The average pulse pressure was 50. No correlation between blood-pressure or pulse-pressure levels and the severity of the cerebral manifestations was possible.

Electrocardiograms were obtained in 13 cases during paroxysms of tachycardia. These identified the origin of the impulse as nodal in 7 cases, ventricular in 3, auricular in 1 case and in 2 cases the abnormal rhythm proved to be auricular flutter. Comparing this grouping of cases with that shown by the electrocardiograms taken in 102 cases, it was found that cerebral manifestations were present in 60 per cent of cases in which the impulse originated in the ventricle, in 41 per cent of the cases of nodal origin, in 25 per cent of the cases of auricular origin, and in 6 per cent of the cases in which auricular flutter was present. It seems significant that these manifestations appeared more often in cases in which the origin of the stimulus and its propagation over the heart showed the greatest deviation from normal.

Thirteen patients were heard from after a period of from one and one-half to ten years after examination; 9 were still subject

to attacks of paroxysmal tachycardia. Four reported that their attacks had ceased. Ten said that they had experienced no symptoms of cardiac decompensation since their examination. One had suffered from alarming cardiac decompensation during his paroxysms of tachycardia.

The cerebral manifestations occurring in this series of cases may be grouped according to severity. The mildest and most common symptom was vertigo, present in 8 cases. Next in importance was temporary blindness, occurring in 6 cases. In 5 cases the patients fell during attacks but were not unconscious. In 4 cases syncopal attacks occurred during seizures. In 2 cases the seizures were epileptiform in type. It is interesting to note that these symptoms were interchangeable, the same patient exhibiting various symptoms in the same or in different paroxysms.

Attacks of paroxysmal tachycardia were not invariably attended by cerebral symptoms. The presence of cerebral manifestations does not affect the prognosis of paroxysmal tachycardia. In general the prognosis is good if no serious organic heart disease is present.

Illustrative Cases. CASE I.—*Paroxysmal nodal tachycardia with vertigo.* A man, aged sixty-two years, had been subject to severe attacks of vertigo for the last four years. He recalled, only after direct questioning, that these attacks were attended by sudden seizures of tachycardia. The blood Wassermann reaction was positive, and signs of syphilitic aortitis were present. No radial pulse could be obtained in the right arm, but collateral circulation was well established. There was marked arteriosclerosis. After the patient had been under observation a few days severe vertigo developed. The pulse rate was 160, and an electrocardiogram taken during the attack identified the paroxysm as nodal tachycardia with a P–R interval of zero and a cardiac rate of 150. The vertigo ceased when the heart resumed its normal rate.

CASE II.—*Ventricular paroxysmal tachycardia with blindness.* A man, aged thirty-four years, complained of attacks of vertigo and blindness, followed by an attack of rapid heart action, which began two months previously. The family history was unimportant except for migraine headaches. He used tobacco in excess and drank much coffee. He had had occasional attacks of tonsillitis, and had suffered from migraine headaches, but no relation between the headaches and the attacks of rapid heart action was noted. In a typical attack he first became totally blind and dizzy for a few seconds, after which "the heart ran away with itself." He felt very weak during an attack, was bathed in a cold perspiration and was quite pale. The attacks lasted about four hours and ceased after he had vomited. The electrocardiogram taken during an attack showed ventricular tachycardia with a rate of 247. General

physical examination was negative, except for infected tonsils; these were removed. Three years later the patient was not having attacks, and gave no symptoms of myocardial failure.

CASE III.—*Paroxysmal auricular tachycardia with syncope.* A woman, aged twenty-four years, came to the clinic because of irregular heart action. Her family history was not significant. She had had three attacks of pneumonia during the last four years. Seven years before she had first noted that the heart seemed to "skip beats," then "flutter" a few seconds, and in one attack her physician said her heart beat at the rate of 140 a minute for three hours. Attacks were attended by a sense of choking, with a feeling that a ball from the chest went up into the throat and breathing was difficult. Occasionally during attacks the patient fainted, but she never fell, as she always had time to get to a chair or bed. The fainting usually occurred as the attack was subsiding. An electrocardiogram taken during an attack showed auricular tachycardia with a rate of 200. Physical examination showed that the heart was markedly enlarged, and that there was mitral stenosis. The systolic blood pressure was 120 and the diastolic 86. There were no other significant findings except diseased tonsils. A diagnosis was made of paroxysmal tachycardia with epileptiform seizures, but the attacks were characteristic of syncope rather than an epileptiform episode. The subsequent course of this case was not learned as the patient could not be traced four years later.

CASE IV.—*Paroxysmal nodal tachycardia with vertigo and loss of consciousness.* A man, aged fifty-three years, complained of attacks of vertigo and loss of consciousness. His family history was unimportant. He had had la grippe and tonsillitis. In 1907 he was first seized with vertigo and fell, but was not unconscious. The attacks were of short duration and recurred until 1915. The tonsils were then removed and he was free from attacks until two years later. The attacks were presaged by a sense of pressure in the stomach, after which the patient fell and became unconscious. He never injured himself and never "frothed at the mouth." After the spells he perspired freely and felt weak. The general physical examination was negative except for dental sepsis. An electrocardiogram taken during an attack revealed a nodal tachycardia with a cardiac rate of 190. The patient was alive two years later, but no information relative to further attacks was obtainable.

CASE V.—*Paroxysmal tachycardia with epileptiform seizures, blurred vision and hemianopsia.* A man, aged twenty-eight years, had been subject to convulsions for five years. His first seizure occurred while he was shoveling coal and was initiated by blurred vision, after which he fell and became rigid. He was weak for a day or so, but there was no headache or drowsiness. Two more

such seizures occurred at intervals of three weeks, then for a period of two years there was no further trouble. The last attack occurred six months before examination. The sequence of events in an attack consisted of the sudden onset of rapid heart action, hemianopsia, loss of vision and loss of consciousness. An attack might proceed only as far as the stage of hemianopsia, when it would suddenly cease, and the dim vision clear like the raising of a mist. He said he could sometimes tell when an attack was coming on and could prevent it by pressing deeply in front of the sternomastoid muscle. Physical examination was negative, except that the patient was of an eunuchoid type. There were no findings indicative of cardiac disease. A detailed neurologic examination revealed no organic disease. The diagnosis was paroxysmal tachycardia with symptomatic epileptiform seizures.

CASE VI.—*Paroxysmal tachycardia with convulsions and pulmonary edema.* A man, aged twenty-nine years, came to the Clinic complaining of spells of unconsciousness and convulsions. His family history was not significant. He had had influenza and tonsillitis. The tonsils had been removed one year before his examination here. He drank much coffee and used tobacco moderately. His first attack of unconsciousness came on three years before his examination, and attacks had recurred at intervals of from one to six months. There was no aura, but for a day or two before the last two attacks he had felt unusually nervous and emotional. In attacks the patient suddenly became totally unconscious, fell and had general convulsions. His wife said that he chewed his tongue, but he had never injured it. There was no loss of control of the bladder or rectal sphincters in an attack. The patient sometimes became semiconscious, and quickly lapsed back into unconsciousness. The attack ended as soon as he succeeded in vomiting. It left him weak and nervous, but he did not have headache and was not sleepy. His seizures lasted from a few hours to three days. In the attack lasting three days he was cyanotic, there was abundant, blood-tinged, foamy sputum, dyspnea was alarming and the chest was full of rales. The heart beat very rapidly during the attacks. Electrocardiographic tracings taken during the spells of rapid heart action identified the attacks as paroxysmal tachycardia. On close questioning the patient recalled that he had had attacks of rapid heart action since childhood, which were usually controlled by taking a deep breath and holding it. The convulsions were invariably associated with a very rapid pulse, but there were many paroxysms of tachycardia without convulsions or loss of consciousness.

The heart was found to be enlarged on physical examination. The classical signs of mitral endocarditis with stenosis and regurgitation were present. (The electrocardiogram taken in an interval between attacks showed a rate of 86, right ventricular preponder-

ance and slurring of the *Q–R–S* complexes in Derivations II and III.) Physical examination was otherwise negative. A neurologic examination showed no objective evidence of a pathologic process in the central nervous system, and a diagnosis of symptomatic epilepsy associated with paroxysmal tachycardia was made.

Discussion. Observation of a patient exhibiting cerebral manifestations during an attack of paroxysmal tachycardia is the only means of making an absolute diagnosis. However, from a careful history the association of cerebral symptoms with the attacks can be established with reasonable assurance if one has a knowledge of the characteristics of paroxysmal tachycardia, the foremost of which is its sudden onset and abrupt termination. The heart rate is usually more than 140 beats a minute. Patients are likely to consider excitement, exertion and especially flatulence from indiscretions in diet, as exciting causes. Patients often say that they felt as if the heart had stopped or as if it "turned over" in the chest and then began to race at top speed. Their means of stopping an attack is of diagnostic value, and includes vomiting, holding the breath, deep breathing and pressure over the carotid sheath. They are frequently weak following a seizure but do not complain of headache or drowsiness.

The distinction of the epileptiform seizures exhibited in this group from idiopathic epilepsy depends on the establishment, by history or observation, of the invariable association of the epileptiform seizures with attacks having the characteristics of paroxysmal tachycardia, although the converse association need not necessarily exist. In contrast with true epilepsy, the patients have no aura preceding their attacks except those symptoms referable to the heart at the inception of its new rhythm. They do not injure themselves nor froth at the mouth. Involuntary defecation and urination do not occur. There is no aftermath of headaches and somnolence as following epilepsy. The lividity seen in epilepsy may be replaced by pallor, and the patients complain of much weakness after their attacks.

Cerebral anemia seems the most reasonable explanation for the cerebral manifestations. Henderson, Scarbrough and Chillingworth have shown that a moderately slow pulse rate is essential for normal filling of the ventricles. At the excessively rapid rate the filling, and hence the output of the ventricles, is below normal. This causes a fall in blood pressure. The symptoms that ensue include pallor, weakness, sweating, vertigo and in some cases syncope—symptoms that are encountered in cerebral anemia from other causes, such as shock and hemorrhage. Whether symptoms indicating cerebral anemia will be present in a given case probably depends on various factors. Esmein and Donzelot argued that the diminished blood supply was not sufficient unless it occurred in an

individual representing a "neuropathic soil" and who gave an exaggerated reaction of the nerve centers to ischemia. The occurrence of generalized arteriosclerosis in a number of the cases here reported seems a possible factor in determining the occurrence of cerebral symptoms. First of all, sclerosis of the cerebral vessels would tend to increase the possibility of cerebral ischemia. Furthermore, the heart with sclerotic vessels would tire more readily than one with normal bloodvessels, and thus affect blood pressure adversely. The predominance of cerebral symptoms in cases in which the origin of the impulse and its propagation in the heart showed the greatest deviation from normal has been pointed out. This suggests that, besides the pulse rate, a cardiac mechanism plays an important part, and that ventricular function and hence cerebral circulation are more likly to be seriously handicapped when there is a maximal incoördination of cardiac activity. Granted the defective filling of the ventricle imposed by the rapid heart rate, it is reasonable to believe that mitral stenosis would further accentuate this defect because of the narrowing of the mitral valve, a mechanism which probably obtained in 1 case reported here. Thus it seems likely that various factors by their influence on blood pressure or circulation rate may determine the occurrence of cerebral anemia in a given case.

Summary and Conclusions. 1. Cerebral manifestations, consisting of vertigo, hemianopsia, temporary blindness, fainting, falling with or without loss of consciousness, and epileptiform seizures, occurred in 15 of 104 cases of paroxysmal tachycardia that were studied. The presence of these symptoms requires that paroxysmal tachycardia be carefully considered.

2. Cerebral manifestations in attacks of paroxysmal tachycardia occurred most frequently in cases in which the origin of the impulse and its propagation in the heart varied the greatest from normal.

3. The presence of these manifestations does not affect the prognosis in attacks of paroxysmal tachycardia. The prognosis depends on the type and degree of the underlying cardiac damage.

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A CAUSE OF ESSENTIAL HYPOTENSION.

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The etiology of essential hypotension has in the recent past been the subject of vast research resulting in many hypotheses, yet today its cause is still unknown, and but little progress has been made in the alleviation of its concomitant distressing symptoms. It is not intended in this article to consider low arterial pressure resulting from the acute infectious diseases, Addison's disease, anaphylactic shock, a defective myocardium or a deficiency of the cardiovascular system, and so forth, but to discuss the so-called "essential hypotension."

Definition. The term "essential hypotension" has been variously defined by different writers. Riesman[1] has named it "constitutional hypotension." He claims that it is found as a permanent feature in persons who are otherwise in fairly good health; and that as a result they are subject to colds, and have cold hands and feet, "poor circulation," and exhaust physically and mentally very quickly. Friedländer[2] claims that hypotension may justly be said to be a symptom rather than a disease, and that it is not even established, that it is always a manifestation of a diseased bodily state. He also claims: "It must be admitted at once that, for many of these hypotension states we have no adequate explanation." Mosenthal[3] writes that, because of its unknown etiology, it is often largely described during the World War under the term neurocardioasthenia, and that it is difficult to be certain whether the low blood pressure is a cause or an effect of the malady.

Barach[4] describes it thus: "A condition in which hypotension constitutes the most marked abnormality in the individual."

It is generally agreed that a systolic pressure of, or less than, 110 mm., denotes hypotension in the adult male. It is but rarely that a systolic pressure of 110 mm., gives the characteristic symptoms of hypotension, but a slight fall from that level will nearly always be followed by some subjective symptoms.

Frequency. The combined figures of Alvarez[5] and Barach[4] give 279 cases of hypotension (below 110 mm.), in a group of 10,142 male subjects, making an incidence of 3.55 per cent. I have found, both in hospital and private practice, a much greater proportion of these cases of essential hypotension in the male. Its frequency is approximately 8 to 10 per cent in the female adult. It must be understood that my observations were made on a group of patients of whom a large proportion were splanchnoptotics.

Etiologic Hypotheses of Essential Hypotension. Various postulates as to the etiology of essential hypotension have been advanced

from time to time. The most reasonable hypothesis, from an endocrinological standpoint, is exhaustion of the suprarenal glands. Friedländer[2] recently concludes that histamins and other vasodilatins are constantly produced in the body, but as a working hypothesis, not proved as yet, persistent low blood pressure in many conditions may be due to poisoning of the capillaries by histamin or histamin-like substances. He states that considerable evidence has been accumulated to justify the assumption of such a view, though admittedly, much work must be done before the hypothesis may be said to rest on the basis of established fact. Barach[4] recently advanced his hypothesis of respiratory deficit and decreased oxidation as a cause of arterial hypotension.

In my experience, I may say, all cases of so-called "essential hypotension," that is, cases in which there were no apparent etiologic factors for the low systolic blood pressure, were found accompanied by an elongated ascending aorta, by an attenuated aortic hemicircle, and by a drop heart. All the evidence, both from my individual cases, and from correlation of cases in the literature, seem to point significantly to the deduction that essential hypotension must be considered a symptom of splanchnoptosis, and that it is generally found in the so-called asthenic or hyposthenic type of men.

Symptomatology. The syndrome complex accompanying essential hypotension is so peculiar, that it is frequently possible to predict the hypotension by the subjective symptoms, and the subjective symptoms by the hypotension. The lowering of the arterial pressure causes typical symptoms, but the fact must not be overlooked that in my experience essential hypotension is usually found in a distinctive type of stature and of bodily conformation (the splanchnoptotics or the asthenics), and that many symptoms may be attributed to the latter and not to the low blood pressure.

Goodman,[6] Lawrence,[7] Roberts,[8] and others, rightly claim that the chief symptoms of essential hypotension, are physical and mental exhaustion and lack of endurance. Throughout literature we read of mental and physical asthenia, neurasthenia, asthenia universalis congenita, neurocardiac asthenia, neurocirculatory asthenia, and other terms especially coined since the World War, all meaning the same thing, and that is, essential hypotension, drop heart and splanchnoptosis.

Mental and physical fatigue are the predominant symptoms of essential hypotension, which, I think, can safely be attributed to the lowered arterial pressure. These patients tire easily, and it is with the greatest difficulty that they can concentrate attention upon their work. Memory is thereby impaired, so much so, that these subjects are mental defectives, to the degree that, they cannot perform the day's work of their more fortunate brothers. They feel the need of mental and physical rest, and the intensity of their symptoms are alleviated in the recumbent position, and increased in the

upright. Vertigo, a sensation of lightness and voidness in the head, and headaches, are frequently present in hypotension, especially in women. These subjects are as rule hypochondriacs and neurotics. Marked vasomotor disturbances are usually associated with essential hypotension, the extremities are usually cold, cyanosed moist, clammy and numb. The palpable arteries are contracted,

FIG. 1.—Characteristic statural type of essential hypotensive subjects.

roll under the finger, and may be mistaken for arteriosclerosis, from which it can be differentiated by the height of the arterial pressure. The skin and conjunctivæ are pale and present an anemic appearance, which is frequently diagnosed as some serious anemia, but the blood is generally normal in its count and hemoglobin content.

The characteristic features of the statural types of these hypo-

tensive subjects are usually that they are tall and slender, long necked, low narrow chested with sunken epigastrium and protuberant and hanging abdomen, the lumbar spine is practically straight, or its dorsal curvature slightly convex instead of concave (Fig. 1). They are usually emaciated and according to Barach,[4] hypotension occurs in lighter weight individuals, of the hyposthenic and asthenic build, having small chest capacity, and in those who are distinctly of the nonathletic type.

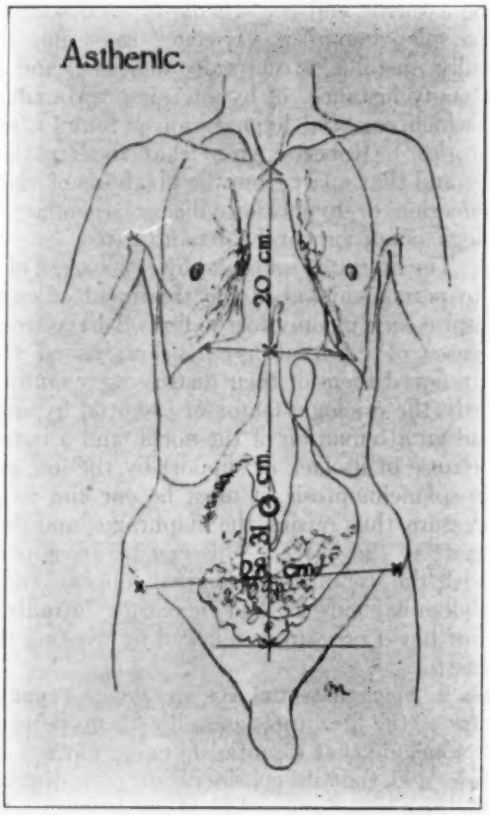

FIG. 2.—The visceral form and arrangement of the asthenic or splanchnoptotic. (Taken from Mills.)

Those elongated flattened chests of the paralytic type so commonly found in splanchnoptosis, and I may say in essential hypotension, have narrow but long sternums, with small or absent ensiform. The costal angle is very acute and the ribs slant downward. The diaphragm is pushed down and flattened. The weight of the poorly supported pericardial sac and its contents draws the heart and the vessels at its base to the median line and

causes them to undergo a certain elongation and attenuation (Fig. 2). The stomach is elongated, the liver slightly ptosed, and the colon displaced. The size, shape and position of the thoracic and abdominal organs depend on the bodily conformation of the subject.

Larimore[9] in his observation on the blood pressure of 417 male and female workers found that hypotension was present in 9.7 per cent of the sthenic and 68 per cent of the asthenic males, and in 18.8 per cent of the sthenic and in 64.5 per cent of the asthenic females. The asthenic and the sthenic types described by Mills[10] correspond to splanchnoptosis. Greene[11] says that this more or less functionally unstable, structurally deficient, and nonresistent group yields many instances of hypotension. Martini has labeled the cases in which essential hypotension is found: "neurasthenics and visceroptotics." Roberts[8] wrote that these patients are not neurasthenics, and that apart from the diagnosis of visceroptosis or mild focal infection or hypochlorhydia or secondary anemia, no active pathologic condition can be demonstrated.

Treatment. The literature on this subject is barren of any encouragement as to permanent aid in the treatment of essential hypotension. Despite such gloomy forebodings, I have treated successfully these cases of essential hypotension, raised their systolic pressure and relieved them of their distressing symptoms.

As frequently the etiologic factor of essential hypotension is an elongation and an attenuation of the aorta, and a narrowing of its hemicircle, because of its lack of support by the low and flattened diaphragm in splanchnoptosis, it must be our aim to increase the abdominal pressure, thus raising the diaphragm, and thereby giving a better support to the heart. This can be accomplished in two ways: first, with the use of an abdominal support, and second, by developing abdominal muscles and increasing intraäbdominal fat. Usually the low blood pressure is relieved by treating the concomitant splanchnoptosis.

Bodily Types in which Essential Hypotension is Found. From the previous review of the literature, as well as from personal observations, I must conclude that essential hypotension is a symptom of splanchnoptosis, and that its consideration as a distinct nosologic entity is unjustified, both from a clinical and anatomical standpoint.

The stocky built, wide chested, high diaphragmed individuals, with large but short sternums, have a wide transverse diameter of the great bloodvessels (Fig. 3). C. L. Martin[12] says that it seems that a high diaphragm is in itself a cause of widening of the aortic arch. These subjects belong to the hypersthenic type and, as far as I can determine, are immune from "essential hypotension."*

* We doubt if this statement will pass unchallenged. We ourselves have seen persons of this type with arterial pressures of less than 110 mm. with no apparent etiologic factor, *i. e.*, essential hypotension.—Ed.

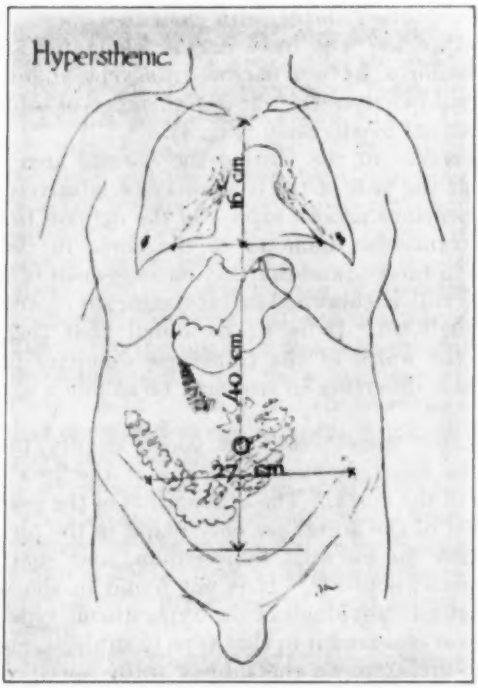

FIG. 3.—The hypersthenic type. (Taken from Mills.)

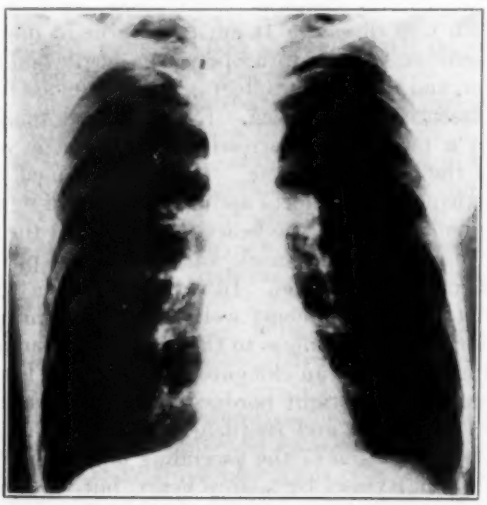

FIG. 4.—Roentgenograph of chest of essential hypotensive subject. Elongated and attenuated ascending aorta, small aortic hemicircle, drop heart.

Those of enteroptotic habitus, with elongated chests, slanting ribs, narrow costal angles, who have narrow elongated sternums with diminutive ensiform, have a narrow transverse diameter over the area of the great bloodvessels. It is in this class of subjects in whom are found essential hypotension (Fig. 4).

These differences in the size of the normal area of the great bloodvessels at the base of the heart may be relatively great. The writer[13] in a previous article, expressed the opinion that the size of the normal transverse diameter of the aorta in the adult male varies from 3 to 4.5 cm.; and that any measurement of that diameter more than 4.5 cm., is abnormal and is significant of some underlying pathologic condition. It is to be noted that there is a great variation in the width of the transverse diameter of the normal aortic arch; this difference in size may be as much as 1.5 cm. (Fig. 2, 3).

As a rule, the same conditions which modify the shape and position of the heart, influence the size of the great bloodvessels and the arch of the aorta. The attenuation of the aortic hemicircle and elongation of the aorta, are only found in the physical type of men susceptible to essential hypotension, and that type is the sthenic or splanchnoptotic. It is not found in the wide chested, high diaphragmed individuals of the hypersthenic type; at least, the writer has never observed it in that type of subjects, and a thorough search of the literature on the subject states specifically that it is found in the asthenic or visceroptotics, and also the histories of these published cases give all the ear marks of that specific statural condition. Furthermore, some observers have written that low blood pressure denotes incipient tuberculosis, as it is frequently associated with that disease. It must be borne in mind, however, that the asthenic or visceroptotics present a fertile soil for tuberculosus infection, and thereby the effect is misundertsood for the cause.

Cause of Essential Hypotension. Essential hypotension may be attributed to a mechanical narrowing of the aortic arch and an elongation of the ascending aorta. It was mentioned that the difference in the length of the aorta and in the width of its arch depend upon the degree of support the heart receives from the diaphragm; the position of the phrenic muscle varies with the physical bodily conformation of the individual. In a thorax with a wide sternum and a high diaphragm (the heart well supported), the right border of the superior vena cava bulges to the right and assumes a distinct convexity (Fig. 3), but in an elongated chest with a low diaphragm (the heart hanging) the right border of the vena cava straightens out, loses its convexity and frequently becomes slightly concave (Fig. 2). The elongation of the ascending aorta cannot be due to a stretching of that vessel by a drop heart, but the weight of that organ causes a lowering and a contraction of the aortic hemicircle. In other words, the arch is narrowed in cases of vertical hearts, and widened in well supported oblique hearts.

The low blood pressure is due to the following mechanical factors: (1) the ascending aorta is lengthened, and the distance from the heart to the upper portion of the arch of the aorta is thus considerably increased; (2) the smaller hemicircle of the arch of the aorta increases the resistance to the flow of blood (Fig. 4). While the cardiac pressure may be amply sufficient to maintain a normal systolic pressure under normal conditions, the increased resistance to the flow of blood offered by a narrow aortic arch, and to a certain extent by an elongated ascending aorta, will cause a diminution of 10 to 30 mm., in the systolic pressure.

Essential hypotension is I believe, due to a mechanical factor based on a mechanical principle. If the heart pressure in two individuals is the same, the one who has a wide aortic hemicircle and a short ascending aorta will have arteries well filled with blood, and normal systolic pressure, and the one who has a narrow aortic arch and an elongated ascending aorta, will have but partially filled arteries and a low systolic pressure.

Essential hypertension is not found in every case of splanchnoptosis, but any factor which diminishes abdominal tension, such as, loss of fat, weakness of the abdominal parietes, especially after parturition, or during the wasting infectious diseases, predisposes the subject to low systolic pressure, and has a tendency to reduce the systolic pressure.

The following cardiovascular characteristics are found in essential hypotension: (1) The arch of the aorta is pulled down, its hemicircle is small, and the size of the transverse diameter of the area of the great bloodvessels varies from 3.5 to 4.5 cm.; (2) the right border of the superior vena cava is straight or sometimes slightly concave; (3) the heart is vertical and poorly supported and its transverse diameter is small, and together with its great vessels appears drawn out and greatly elongated.

Comment. This thesis is based on the following hydraulic principles: "When water flows around a bend, loss of head occurs due to the fact that rotational energy is imparted to the water in passing around it. This loss depends on the DIAMETER of the pipe, on the RADIUS of the BEND, and on the ANGLE of DEVIATION."[14]

Also: "The longer the pipe is, the greater the percentage energy will be used in overcoming friction, and the smaller will be the FINAL VELOCITY ENERGY."[15]

Conclusions. 1. All hypotheses heretofore advanced as to the etiology of essential hypotension have been either unproved, refuted or impractical.

2. Essential hypotension is usually found in the asthenics or the splanchnoptotics: it is a symptom of splanchnoptosis.

3. Its characteristic symptomatology is commonly found in the asthenics or splanchnoptotics, and but very rarely, if ever, in the hypersthenics.

4. The low blood pressure is raised by the treatment of splanchnoptosis, *i. e.*, abdominal support, the strengthening of the abdominal muscles and the increase of the intraäbdominal fat. The use of organotherapy has proved to be unsuccessful in correcting the hypotension.

5. It is met in cases having an elongation of the ascending aorta, a narrowing of its hemicircle, and a heart poorly supported by the diaphragm (drop heart). (Fig. 4.)

6. It answers the hydraulic principles, the longer the pipe and the smaller the radius of the bend, the smaller will be the final velocity energy; or in men, the longer the ascending aorta, the narrower the diameter of the aortic arch, the heart pressure being equal, the lower the systolic blood pressure.

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SPLANCHNIC DYSPEPSIA. A GASTROINTESTINAL SYNDROME OF CIRCULATORY ORIGIN.

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(Read before the Medical Society of the District of Columbia, October 14, 1925.)

The purpose of this paper is to direct attention to a syndrome occurring in asthenic patients and often referred to by them as "indigestion."

It is not digestion which is disturbed, but the circulation.

The first requirement in a discussion which is intended to separate as a clinical entity, one symptom complex from a larger and more heterogeneous group, is classification. With functional gastro-intestinal disturbances, this is necessarily on a clinical, rather than a pathologic basis, and therefore, definition cannot be as precise as desired. However, the established classification is sufficiently clear for clinical work, and departure from, or addition to, the accepted forms should not be made without justification.

Here it is only necessary to state that the following recognized clinical forms are noted as not included in this discussion:

1. Disturbance secondary to recognizable constitutional diseases.
2. Enteroptosis.
3. Reflex disturbances from other abdominal and pelvic organs.
4. Dyspeptic manifestations of the neuroses and psychoneroses, such as anxiety neuroses, cyclothymia, and the like.

The conception most nearly approximating the one to be presented, and the only one I have found, is given by W. Egbert Robertson in Sajous' *Analytic Cyclopedia of Practical Medicine;*[1] he states, writing on visceroptosis:

"Probably many of the phenomena can be explained by disturbances in the abdominal circulation due to tension upon the vessels, the result of prolapse with consequent lowering of the organic function; in addition there are likely to be present symptoms resulting from vasomotor disturbances due to stretching of the splanchnics, as well as cardiac disturbances or motor disturbances of the stomach and small bowel, induced by vagus irritation."

If the syndrome which I shall describe, does not deserve a class of its own, but must be placed under the manifestations of enteroptosis, then the discussion will at least furnish a rational explanation for a group of puzzling symptoms, and suggest a therapeutic attack nearer to the origin than has heretofore been the general practice.

The complaint in the patients' words is of "biliousness," "constipation," "autointoxication," "nervousness," and "heart attacks from gas." When analyzed, the condition is found to be entirely different from what the complaint would indicate: Constipation, becomes "a feeling of weight, heaviness or fullness in the abdomen," "a feeling as if something were there," "All is dead inside."

These sensations are temporarily relieved by a laxative or enemas, but return after a few hours. The patient takes laxatives and enemas so frequently that he does not know what the bowels will do voluntarily, and when asked why he takes laxatives when the bowels have already moved, he says, "They have not moved sufficiently. It feels as if something were still there."

If we inquire what symptoms the autointoxication produces, we hear complaint of mental dullness, inability to concentrate the attention, mental lethargy and physical fatiguability. The "heart

attacks" are unpleasant sensations about the sternum or heart area, "inside trembling," "poor circulation," "cold and clammy extremities," "dizziness," "vertigo," "feeling of faintness as if the heart were about to stop," or "its beating is perceptible and annoying;" "Something moves inside." "The heart feels like pouring water out of a jug." "I am about to go away." "Everything is fading." "Cannot get a deep breath." "Must have air." "Something starts from my stomach and goes up to my head." The different patients present their complaint in nearly the same words, and amplify their symptoms with the same illogical interpretations.

These symptoms could be extended infinitely in content and variety, but the more they are elaborated, the more apparent it becomes that they do not belong to the symptom complex of any disease entity described in the textbooks.

In the history there appears, with impressive repetition, the following statements: "I was never strong;" "Always had a weak stomach;" "finished four years school work in three;" "worked way through college;" "supporting invalid mother," that is, some form of effort involving long continued stress, combined with material care, desire ungratified, ambition beyond achievement.

Physically, many of the signs of Stiller's habitus are present, and the lungs are under suspicion. There are undernutrition, frequent colds and loss of weight. Examination in every field, special and general, leaves us where we started; namely, many symptoms, no organs found diseased, though the appendix has been removed in many, and the uterus suspended in some. Of course, the tonsils have been removed, the teeth attended to beyond criticism, and glasses fitted for eye strain.

It is true that some present such a picture that one of the neuroses is diagnosed. Another will be classified as atonic dyspepsia on account of the digestive complaints, or as enteroptosis on the basis of physical appearance. The terms, "weak heart," "thyroid disease," "incipient tuberculosis," "endocrine disturbance," are also used in ticketing these chronic patients.

A striking feature of all of them is the absence of a definite pathologic process according to present standards of diagnosis. Nevertheless, after taking the history, examining and studying several such patients as in a thorough medical survey, one is impressed by the frequent recurrence of the same findings, and the conviction grows, that whatever the diagnosis may be, or should be, they all are suffering and are impaired in health by the same condition.

In the course of study of many such patients I have been impressed by:

1. Their clinical kinship.
2. Absence of demonstrable lesions.
3. Lowered physical tone.

4. That the successful therapeutic approach must lie along other lines than gastrointestinal medication.

The opinion has been formed that the gastrointestinal tract was neither the cause of the illness nor the primary source of the symptoms. Certain frequently recurring findings pointed in another direction. The low blood pressure, large mobile pupils, variability of the pulse rate, vasomotor skin disturbances, sinus arrhythmia, all pointed to the circulatory system.

The article by Crampton[2] led me to make systematic observations on many cases by his method, which was elaborated to indicate the gravity-resisting ability of the circulatory apparatus, especially the extra cardiac factors.

When examined by this method, the patients complaining of the symptoms described are found to have a low index, that is, there is a marked fall in blood pressure and increase in the pulse rate on standing, after lying.

Sometimes, in addition to the measurable objective findings, there are definite subjective symptoms, such as dizziness, faintness and sighing respiration. These latter are recognized as symptoms of cerebral anemia. However, examination of the blood reveals no anemia, and heart lesions, either valvular or myocardial, are absent. The symptoms are promptly relieved by lying down. They are not provoked or made worse by exercise tests, on the contrary, the blood pressure and pulse are often improved, and show less striking variation from the normal on exercise, than they do on simple change of posture.

My hypothesis is, that the above described symptoms are produced by the following mechanism: There is relative vasomotor paresis affecting the peripheral and splanchnic vessels. Since by far the greater volume of such vessels below the heart is in the abdomen, their vasomotor relaxation, leading to a considerable degree of stasis especially on the venous side, definitely increases the weight of the abdominal organs. The effect, however, is most marked in those organs having a mesentery and, therefore, capable of making increased traction on the mesenteric roots and their contained nerves. Such traction naturally leads to further disturbance of vasomotor control, and of specific organic function, notably the motor function of the stomach and bowels by inhibitory influence through the sympathetic nerves.

These motor disturbances, spasticity at one point and relaxation at another, allow a pocketing or accumulation of gas in certain loops of the bowel, producing sensations of fullness and tension: hence, the description, "a feeling as if something were there," or, "everything inside has stopped."

Regular action of the heart is dependent partly upon a constant flow of venous blood to the auricles. Vasomotor relaxation of the splanchnic veins, with consequent venous stasis in this area would

cause a proportionate retardation of the flow to the heart, resulting in disturbances in force and rhythm, which are recognized by the patient as various subjective sensations. The complaint is a mixture of sensations and alarming interpretations.

Naturally, no evidence of organic lesion can be discovered. The same mechanism would produce variations in the cerebral and pulmonary circulation, resulting in sensations of threatened syncope, "I am about to fade away," and, "I cannot get a deep breath." The attacks being temporarily relieved by either laxatives or enemas, the patient naturally attributes relief to an evacuation of the bowels. This is a wrong explanation, which leads to much mistreatment. This is shown by the fact that sometimes relief is experienced before an evacuation occurs.

The patient complains, after several movements, that "all has not come away," "something is still there." The symptoms return within a few hours, not usually a delay of twenty-four hours, as would be the case if due to intestinal stasis. Some of the symptoms, notably those of cardiac, cerebral, respiratory and vasomotor type are too transitory in time and evanescent in character to be brought about by the slow increase and accumulation of the bowel contents. They are of a few minutes' duration and change one into another rapidly. The temporary relief is illusory; the patient's condition and symptoms become worse from day to day and week to week under such management.

The correct explanation of the action of laxatives in these cases is entirely different. Laxatives act by increasing peristalsis, the abstraction of fluid from the bowel wall, or by a combination of these methods. Peristaltic movements of the bowel increases the venous flow, and improves the sluggish circulation. We know that salines are administered for their action in relieving engorgement of the portal circulation. If this is accomplished, circulation is improved. Enemas, even if there is no return but the injected fluid, stimulate peristalsis (as is proven by the expulsion of gas) and so facilitate the emptying of engorged veins. So the laxatives and enemas produce temporary amelioration of some of the symptoms, not by an evacuation of the colon, but because they immediately improve the splanchnic circulation. Their use for this purpose is comparable to the administration of salts to a cyanotic patient with a dilated right heart, instead of performing phlebotomy, and giving digitalis.

The more physiological therapy would be:

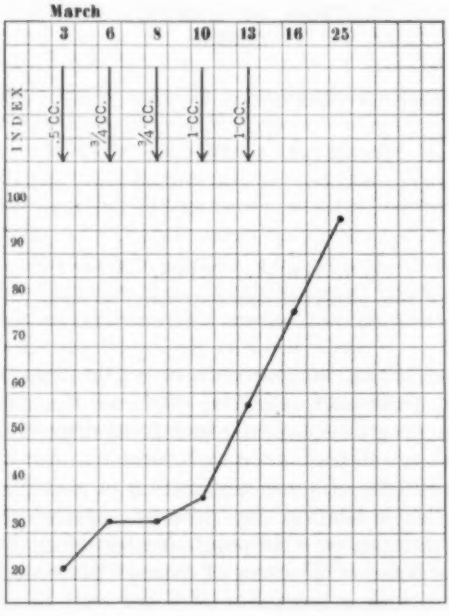
1. Abandon laxatives, enemas and rest cures.
2. Give a bland, laxative, nutritious diet.
3. Adopt measures calculated to improve the hypotonic circulation:

   (*a*) Exercises with exhilaration, alternating with frequent short periods of rest.

(*b*) Properly fitted abdominal support for women with relaxed abdomens.

(*c*) Teach those with inadequate circulatory systems to live and work within their limited capacity.

(*d*) Pituitrin 1 cc., and adrenalin 0.25 cc., given hypodermically, have seemed to be of definite value on the hyposthenic circulation, (see Chart) which shows progressive improvement in the gravity-resisting capacity of the circulatory apparatus as measured by the Crampton index. Note that the improvement is maintained twelve days after the last dose of pituitrin was given.



That the hypothesis here presented should lead to uniformly satisfactory results is not to be expected, but the interpretation given, and the therapeutic approach indicated, represents an effort to restore function by correcting the disturbance as near its origin as present knowledge of cause will permit. The plan has been of definite aid in practice.

Summary. There is described a group of symptoms, often referred to as "indigestion;" due, not to disturbance of the digestive function, but to disorder of the circulation.

The relief experienced after a laxative or enema is attributed to an evacuation of the bowel, but this is erroneous, because relief occurs before the evacuation and the symptoms return within a few hours, before stasis could recur.

The real character of the syndrome is indicated by vasomotor disturbance, imbalance of the sympathetic nervous system and a low Crampton's Index. Remedies should be directed to restoring the tone of the circulatory mechanism, and not to the digestive organs.

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ACUTE PERFORATION OF GASTRIC AND DUODENAL ULCER.

A Study of Sixty-two Consecutive Cases.*

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The diagnosis of the complications of peptic ulcer which demand urgent surgical treatment must be made at the earliest possible moment, as the prognosis depends to a great degree on the number of hours which have elapsed since such complications have occurred. This is especially true of acute perforation of gastric and duodenal ulcers where the indication for prompt surgical interference is imperative. Statistics on this point are furnished by McCreery,[2] who reported a series of 25 cases of acutely perforated gastric and duodenal ulcers, with a mortality of 6 per cent in those operated within twelve hours, a death rate of 60 per cent in those operated after twelve and before twenty-four hours and a mortality of 100 per cent in those undergoing surgical treatment after forty-eight hours. Steichele,[4] in a report of 53 cases of acute perforation of peptic ulcer, states that 6 per cent of the patients died when operated within twelve hours after the onset and that the mortality rose to 86 per cent when there was a delay of fourteen hours or longer.

Our own conclusions, based on a study of 62 consecutive cases of acute perforation of gastric and duodenal ulcer observed by us during the last three years, leads us to the same opinion. The

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total mortality of our entire series was 29 per cent. Thirty-five of the patients were admitted to the hospital in from one to six hours after the onset of their symptoms, and of these 7, or 20 per cent, died. Seventeen patients were admitted in from seven to twelve hours after the onset, and of these 6, or 35.5 per cent, died while 10 were admitted after thirteen or more hours had elapsed, and of these 5, or 50 per cent, died, showing a definite and sharp rise in the mortality rate if operation is delayed for even a few hours.

Among the other interesting features brought out during this study is the fact that, without exception, all of the cases occurred in males. We are unable to explain why there were no females in our large series, since we shall show subsequently that overeating and overexertion play but a minor role in the actual production of the perforation. The greater incidence of ulcer in men as compared with women does not fully explain this feature as the most partial observers do not place the preponderance of ulcer in males at more than three or four times as great as in women. This observation is of importance, however, from the standpoint of diagnosis. We can place greater importance on the possibility of acute perforation of a peptic ulcer as a cause for "acute surgical abdomen" in men than in women, and if our findings are corroborated by further investigation, advantage may be taken of this point in the differential diagnosis of acute abdominal disease occurring with about the same frequency in both sexes.

Another interesting point observed by us is the age at which acute perforation occurred. According to Steichele,[4] acute perforation is most common between the ages of twenty and forty years. Our own series showed that 2 cases occurred at the age of nineteen years; 18 cases occurred between the ages of twenty and thirty years; 17 occurred between the ages of thirty-one and thirty-nine years and 25 at or beyond the age of forty years. We thus see that 37 cases, or nearly 60 per cent, occurred in patients under forty years of age, and that the incidence in persons thirty years of age or younger was 32 per cent. This observation is of importance in the differential diagnosis from acute appendicitis which occurs with such great frequency in younger adults. It is difficult to explain why such a large proportion occurred in younger individuals unless we assume that acute perforation occurs sooner in its course than is commonly supposed. This supposition finds some support in the statement of Gibson,[1] who says that about 25 per cent of cases of acute perforation do not give a history of digestive disturbances before perforation occurred and our own figures show that 19 cases, or 31 per cent, gave no ulcer symptoms before rupture took place. Our interpretation of the patient's statement prior to the occurrence of the perforation was very comprehensive and this, together with the fact that many of our patients did not understand English

very well, detracts greatly from the proper interpretation of this observation. It must be admitted, however, that a large number, possibly one-half, have few or no symptoms before perforation occurs. We also wish to point out in this connection that a large number of patients stated that the pain became much more severe and constant and was uninfluenced by food or alkalies for a few hours or days before perforation occurred.

Equally interesting is the observation, as previously mentioned, that the distention of the stomach by food had apparently little to do as a direct cause of the perforation. The symptoms occurred in from two to four hours after the last meal in 35 cases, or in 56 per cent; in from five to seven hours after the last meal in 8 cases, or in 13 per cent; in from eight or more hours after the last meal in 6 cases, or in 10 per cent; in less than two hours after the last meal in only 10 cases, or in 16 per cent. No data on this point were obtained in 3 cases. From this it is seen that perforation occurred in about 79 per cent, or in four-fifths of all cases, after two hours or more had elapsed after the last meal. It is possible that the contractions of the nearly or completely emptied stomach, or that the contents remaining in the antrum, had something to do with the actual perforation, but we believe that distention alone by food plays a comparatively minor role.

A similar observation was made relative to the effect of unusual exertion or physical strain as a possible direct cause for the perforation. There was no history of such strain or exertion in 58 patients, or in 94 per cent of our series. On the other hand, perforation occurred during sleep in 5 patients, or in 8 per cent. In only 2 patients was there a history of unusual exertion shortly before perforation.

Our study of the clinical features of acute perforation of gastric and duodenal ulcer revealed that nearly all patients complained of a sudden, severe and overwhelming pain in the upper part of the abdomen; constant and unaffected by food or alkalies and associated with prostration, vomiting after the onset of the pain, leukocytosis, tenderness and boardlike rigidity of the abdominal muscles. Radiation of the pain to the shoulders as described by Ohelecker[3] was noted in only 6 cases, but it is possible that the actual incidence of this shoulder pain was more frequent, as we did not question many of our patients relative to this point. The diagnosis in the early stages, when the above-described picture was present, was apparently very easy, as a correct diagnosis was made before operation in 53 cases, or in 85 per cent. When the patients were seen in the later stages, especially after general peritonitis or meteorism had set in, the diagnosis was much more difficult, as the seat of greatest pain and tenderness was then likely to be in the right lower quadrant instead of in the upper part of the abdomen, and the entire picture was clouded unless free intraperitoneal air

was detected on fluoroscopic examination, according to the procedure described by Vaughan and Brams,[5] in which, without the use of a contrast meal or any preparation of the patient, free intraperitoneal air can be detected in 87 per cent of cases of acute perforation. The patient is simply placed on a cart and, with the screen over the abdomen, the regions between the liver and diaphragm and the space between the liver and the right abdominal wall, and also the region between the spleen and the left wall of the abdomen, are carefully examined. The patient is then turned first on the left side, and the space between the liver and right abdominal wall is examined for air, which can be very easily detected even if present in only small quantities. Further examination is not necessary if air is found, but it may be necessary to examine the patient when on his right side for air between the spleen and the left abdominal wall and perhaps in the sitting position when air may be seen between the liver and the under surface of the diaphragm. The sign is of value because it is present early, at times two hours after the perforation occurs, and because the finding of air in the peritoneal cavity is of great significance in the recognition of perforation of a peptic ulcer.

The conditions for which acute perforation were most often mistaken were acute appendicitis and intestinal obstruction. One patient had both a strangulation of the jejunum and a perforated duodenal ulcer. The strangulation in this patient occurred in an opening in the transverse mesocolon made at a previous date, when a posterior gastroenterostomy was performed for the cure of the duodenal ulcer which eventually was found ruptured. On the whole, the errors were infrequent, and we again wish to point out that acute perforation is not difficult to recognize, providing the condition is kept in mind and if we remember that a large number of these patients do not have previous symptoms suggestive of peptic ulcer.

Another symptom to which attention was paid was vomiting. This was present in all but 6 cases; it always came after the onset of the pain, was seldom severe and hematemesis was not observed in a single case. It may be of interest to mention that vomiting had no effect on the pain in contrast to the relief previously experienced when the ulcer had not yet perforated.

A study of the leukocyte count in this series showed that a definite leukocytosis was present in 39 cases, or in 63 per cent; a normal count was found in 7 cases, or in about 10 per cent; a white cell count was not made in the remainder, as it was not necessary for the purpose of diagnosis. The average count in all cases where it was made was 16,000. Of the cases showing a low or normal white count, 6 died and 1 recovered, showing that some conclusions may be drawn from the white cell count relative to the ultimate prognosis.

The type of ulcer encountered at operation did not seem to have a great effect on the mortality rate, in contrast to the report of C. L. Gibson,[1] who states that the death rate in perforated gastric ulcer is almost double that in duodenal. In our series of 62 cases, 36 were gastric and 26 were duodenal. Recovery occurred in 70 per cent of perforated gastric ulcer and in 73 per cent of perforated duodenal ulcer.

The type of operation most useful in our hands was simple closure of the perforation with covering of the area with omentum. More detailed operations were performed at a later date, when the condition of the patient was much more favorable for recovery, but more complicated procedures were sometimes necessary in the presence of marked stenosis or other mechanical difficulties at the site of perforation. The question of drainage is not settled, but we did not drain in about one-half of the cases, including many in which free fluid was present in the peritoneal cavity at the time of operation.

Conclusions. 1. In a series of 62 consecutive cases of acute perforation of gastric and duodenal ulcer, proved at operation, every patient was a male. This observation may be of value in the diagnosis of surgical emergencies of the abdomen.

2. Sixty per cent of our patients were under forty years of age and 32 per cent were thirty years old or younger.

3. Overdistention of the stomach by food or unusual exertion had comparatively little to do with actual rupture. Perforation occurred during sleep in 5 patients.

4. The clinical picture in the early stages was clear cut, so that a correct diagnosis was made in 85 per cent of the cases before operation. The clinical features are obscured later in the course by the resulting peritonitis and meteorism. The location of the maximum pain and tenderness was then often in the right lower quadrant of the abdomen instead of the epigastrium. The presence of free air in the peritoneal cavity on fluoroscopic examination proved of great help in the diagnosis both in the early and later stages of perforation.

5. Vomiting always occurred after the onset of the pain, and was present in all but 6 cases, but in no case was hematemesis present.

6. Our series showed no marked difference in the mortality rate of gastric and duodenal ulcer. The total death rate was about 29 per cent and rose rapidly with delay before operation.

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SPRUE IN THE TEMPERATE ZONE.

With Report of Case.

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Sprue is recognized occasionally in this climate in persons who have been in tropical and southern regions. The cases reported by various authors have all visited tropical climates, and this has led to the general belief that it was never acquired in the temperate zone. The purpose of this paper is to report an instance where the life history of the patient was known and shows the infection to have occurred in this climate. As it is recognized that as long a period as seventeen years has elapsed in some cases since residence in tropical regions, it becomes necessary to obtain accurate residential history. To dispel an idea of climatic restriction, to recall the disease again to northern physicians' minds, and to show how it may be confounded with pernicious anemia, are sufficient reasons for presentation of this case. It will also create a desire to separate or transfer some of the atypical pernicious anemia cases into sprue, when the Monilia psilosis is an intestinal resident.

Case Report. Mrs. W. J. B., aged thirty years, American, married, consulted me, December 12, 1924, on account of periodical attacks of diarrhea, accompanied by marked weakness, which had been diagnosed eight years previously as pernicious anemia. She was just recovering from an attack which had begun three weeks before. The history elicited the fact that the illness began insidiously at the age of sixteen years by paroxysms of marked weakness, and passage of from three to seven large, grayish, gaseous, painless, odorous stools. At this time her appetite was lost, and she had lost about 3 to 5 pounds. Sore tongue a week before the onset of symptoms or accompanying the onset had been noted. The paroxysms of illness at first were very short, and often within forty-eight hours she felt better, but gradually the periods lengthened into three to four weeks, after which her strength would gradually return. In more recent years the matutinal nature of the stools has been observed, and invariably the unloading of the bowels began around dinner time. The large stool and its foamy nature were observed by the patient. It seemed to her that she passed more than she ate. After several hours she would be free of trouble.

Eight years ago she was minutely studied at a hospital, and diagnosed as a case of pernicious anemia. The spleen was removed, as was commonly done at that time. No improvement resulted, and for some time afterward her blood was examined often. In several

of the paroxysms blood transfusions were made on account of the marked anemia.

The patient was born in Chicago, one of seven daughters, and lived there most of her life. For some years she lived in Cleveland, and for two years in Beloit, Wis. She has not been permitted to travel at all on account of her health. Her birth was normal. She had most of the diseases of childhood. At the age of three years she had "cholera morbus," which lasted for six months. After that her health was poor until puberty, when she became robust. Two years later, however, the present symptoms began. She has not been associated with anyone who had a chronic diarrhea. The family history was negative. Two years ago she married a Christian Scientist. They have no children, and there have been no miscarriages.

The examination showed a woman of light complexion, of small development, moderately undernourished, a trifle pale and tired-looking. Her height was 5 feet 1 inch (24.4 cm.); weight, 95 pounds (43.1 kilo). There was no icterus or lemon-tinged appearance. The mucous membranes of the mouth were a trifle pale, several crowned teeth were present and the tongue was relaxed but not inflamed. A marble-sized enlargement of the isthmus of thyroid was present. The aortic second sound was sharp. The splenectomy scar was present on the abdomen, and some indefinite tenderness was found in the right lower abdomen. The skin was soft, cool and showed loss of fat. Otherwise physical examination, including the nervous system, was negative.

The urine gave a reaction for bile, urobilin and a marked trace of indican was present.

Two blood examinations were made five days apart. Both showed a hemoglobin of 50 per cent (Sahli corrected). The leukocytes on the first examination were 9600; on the second, 9400 per cubic millimeter; red blood cells, 3,050,000 and 3,370,000 per cubic millimeter. The polymorphonuclears were 61 per cent; small lymphocytes, 29 per cent; large lymphocytes, 2 per cent; large mononuclears, 5 per cent; eosinophils, 2 per cent; mast cells, 1 per cent. Eleven normoblasts were seen in counting 250 cells. The cells showed achromia, irregularity in size and shape, and polychromatophilia. The color index was less than 1 in both specimens. The blood picture was that of secondary anemia. After an Ewald meal 195 cc. of gastric content were obtained, which was normal. Roentgen ray examination showed a delay of the meal at the duodenojejunal juncture, but at the end of six hours the meal had entered the cecum. The large bowel contained considerable gas.

The stool after a Schmidt diet was large, greasy in appearance, had a musty odor, was clay-colored, acid in reaction, produced fermentation, contained excess amount of fat, and gave a reaction

for occult blood. Ninety-five per cent of the organisms in the stool were Gram-negative. Bile pigment was present. A specimen of the stool was sent to Dr. Wood, who found the Monilia psilosis present. He informed me that it grew in typical colony formation, produced typical gas with maltose, dextrose and levulose, did not ferment inulin and produced definite pink with Andrade's indicator in dextrose agar. Intravenous injection in a robust rabbit produced death within twenty-four hours. Death occurred before localizing lesions were present at autopsy. Cultures from various organs grew typical moist abundant growth of the psilosis. Sprue was diagnosed.

Since that time an unusual five-month remission of her illness has occurred without any treatment, except mental and physical rest. In November, 1925, an exacerbation was forecasted by a sore tongue. Banana and milk diet, meat diet, general diet with careful preparation of food to avoid intestinal irritation, with dilute hydrochloric acid and pancreatin in enteric coated capsules after meals have been thoroughly tried and found to be ineffective in controlling the course of the remission.

Summary of Case Report. A case of sprue developed in this climate in a patient at the age of sixteen years, producing the typical symptoms and blood changes characteristic of sprue, and even suggested pernicious anemia. If the latter, it would have to be labelled atypical. The yeast typical of the disease, Monilia psilosis, was found in the stool. Motility disturbances in small intestines were present as an underlying predisposing factor in the infection. Evidence of blood destruction was found in the presence of urobilin and bile in urine.

Summary. Sprue can be acquired in a temperate zone.

A patient can live many years with the infection.

A search for Monilia psilosis should be made in every case diagnosed as pernicious anemia.

I am indebted to Dr. Edward Jenner Wood, Wilmington, N. C., for his valuable assistance in culturing the stools for the Monilia psilosis.

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INTERSTITIAL GLAND CELLS IN THE HUMAN OVARY.

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It is the purpose of this paper to report the finding in two human ovaries, each from a different case, of cells identical in appearance with the interstitial gland cells of the testis.

Following Fraenkel,[1] the occurrence of such cells in the human ovary is usually denied, though the presence of interstitial glandular cells in the rabbit,[2] in the bat,[3] in the wood-chuck,[4] and in other mammals is well established. Textbooks of histology show a certain vagueness concerning their occurrence in human ovaries. Schaefer,[5] however, presumably from his own experience states "There are also sometimes to be seen in this situation [the hilum] a number of interstitial cells recalling the interstitial cells of the testis. Similar cells may occur scattered in groups about the stroma."

Among the ovaries of 43 psychotic cases which the writer[6] has recently had occasion to examine, in two ovaries, each from a different case, there was observed a small island of such cells in the hilum, while they were not observed in any other ovary in the series.

The two ovaries in question were from patients diagnosed "senile psychosis." Case I had been mentally ill for five years with symptoms of organic deterioration and depression, dying at the age of seventy-nine years, of a myocardial infarction. Her body hair was scanty, but its pubic distribution was of the feminine type. Histologically, the endocrine glands showed no change that would have distinguished them from the other senile cases, except for the occurrence of the interstitial gland cells in the hilum of the ovary.

Case II, aged seventy-five years at death, had been ill for nine years, the symptoms being those of senile organic deterioration, confusional episodes, and a mild paranoid trend. Death was due to rupture of the heart. The patient had borne two healthy children. During her nine years' residence at the hospital, her weight increased from 115 to 275 pounds. The breasts and external genitalia were senile. Histologically, besides the ordinary senile changes, the thyroid and the adrenal glands showed a lymphoid exudate of moderate degree such as frequently accompanies arteriosclerosis in these organs.

Both cases showed general arteriosclerosis and renal involvement.

Fig. 1 shows the left ovary of Case I with the typical senile changes: thin cortex, thickened bloodvessels, degenerative changes in the vessel walls and in the connective tissue of the central part of the gland. In the hilum is to be seen an island of interstitial gland cells (*i. c.*). Fig. 2 shows these cells in higher magnification;

FIG. 1.—Ovary of Case I. *I.c.*, island of interstitial gland cells. *Pv.*, parovarial tubules.

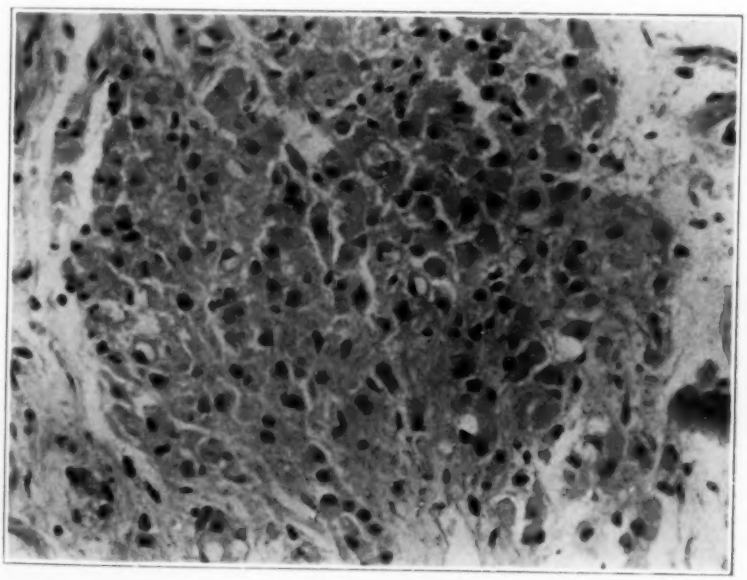

FIG. 2.—High power view of interstitial gland cells from Case I.

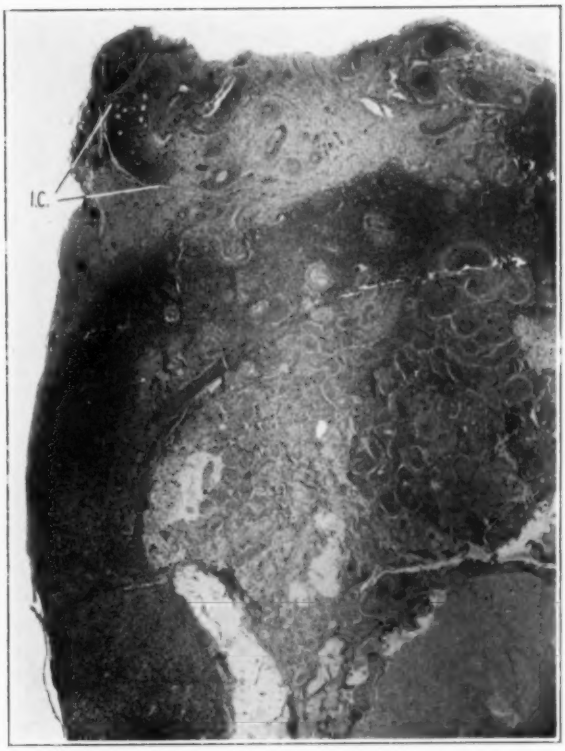

FIG. 3.—Ovary of Case II. *I.c.*, island of interstitial gland cells.

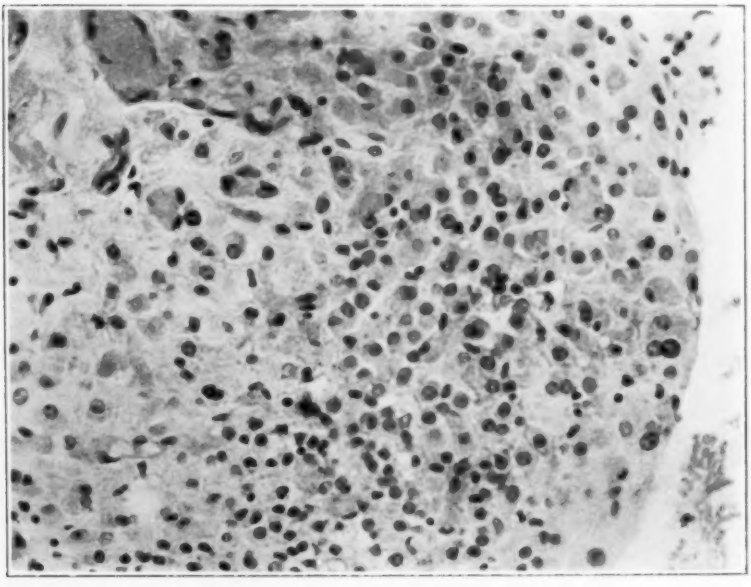

FIG. 4.—High power view of interstitial gland cells of Case II.

it brings out their rather loose pavement arrangement in the island. The nuclei, where not overstained, or dark and shrunken, show the shape and the chromatin distribution characteristic of the interstitial gland cells of the testis. The cytoplasm of these cells is acidophilic and contains a very fine granulation of lipoid pigment.

Fig. 3 shows the senile left ovary of Case II, and again in the hilum region an island of interstitial gland cells (*i. c.*). This figure also shows that the interstitial gland cells are further from the ovary proper than are the parovarial vestiges, marked *pv.* A high power photomicrograph of this section shows interstitial gland cells resembling more closely the homologous cells of the testis than did those in Case I. Here the fixation and the nuclear staining is better, and the round or nearly round nucleus, with its small clumps of chromatin, is quite like the nucleus of the interstitial gland cells seen in the testis. The cytoplasm of these cells is acidophilic, with a stippling of fine lipoid granules.

In these 2 cases, the location of the cells in the hilum, remote from the ovarian stroma and the follicles, and near the vestiges of primitive undifferentiated gonadal structures such as the parovarium, suggests very strongly that they represent a vestigial development of primordial "male" elements. They form, so to speak, a tiny patch of "hermaphroditism;" and the gland is to this infinitesimal extent an "ovotestis."

It is worth noting how close the cell islands lie to the cut made by the pathologist when removing the organ. If 1 mm. less of the ovary had been severed from the mesovarium, the cell islands would have remained in the cadaver, and the ovaries would have shown nothing beyond the ordinary senile picture. Indeed, the apparent scarcity of such islands in human material may be quite accidental: they may, for all we know, be quite common in the mesovarium, yet in routine autopsies escape detection. In our series of 43 cases, at any rate, in spite of special and careful examination, the two ovaries we have described were the sole instances in which these cells were seen.

In the ovaries of psychotic patients, most investigators, including Borberg[7] and Morse,[8] make no mention of the presence or absence of interstitial gland cells. Forster,[9] however, states specifically that they were not to be found in her series of 101 psychotic cases.

In our 2 cases, there seemed to be no functional feature relatable to the presence of the interstitial gland cells. Nothing suggested that they exerted either a "male" or a "female" influence. Obesity in Case II was the only evidence of an endocrine functional disturbance. The psychosis had no obvious connection with the presence of these cells. If there was any tendency to homosexuality, it was not noted in the history. It is, indeed, apparent, even assuming these cells to exert a "male" influence, that there were too few of them in either of the cases for this "male" influence to be manifest;

and furthermore, that whatever "male" or "female" effects they did exert might well have been masked by the general senile changes.

Summary. Among 43 pairs of ovaries from psychotic cases, 2 ovaries, each from a different case, showed in the hilum a small island of cells identical in appearance with the interstitial gland cells of the testis. The clinical diagnosis in both cases was "senile psychosis." No functional features were to be correlated with this finding. If the cells exerted a "male" influence, the fewness of their number, or the presence of general senility, prevented this influence from manifesting itself. The possibility of overlooking the presence of such an island, when the ovary is removed in the usual routine autopsy manner, is pointed out.

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PAIN IN CANCER OF THE BREAST: ITS CLINICAL SIGNIFICANCE.

With Special Reference to Bone Metastases.

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Pain in cancer of the breast is one of the most neglected but nevertheless one of the most important clinical problems, not only from a diagnostic but also from a prognostic and therapeutic standpoint. Although pain in mammary cancer is of extremely rare occurrence in the breast itself during the earlier stages of the development of the primary malignant lesion, its appearance in the breast at any stage is usually an indication that the carcinomatous growth has already undergone secondary degeneration with reactive inflammatory changes in the surrounding tissues. If

the pain is superficial it is usually a warning that ulceration is impending. If deep seated, the presence of pain in the breast may be an ominous sign that the deep structures of the thorax have already been invaded. When in the course of breast cancer local pain is present in the axilla or begins to radiate along the lateral chest wall, evidence of axillary lymph-node invasion will usually be found. Pain, mild or severe, radiating down the arm on the side of the lesion will frequently be found to be due to metastatic invasion of the axillary or supraclavicular lymph nodes with secondary compressive, irritative or inflammatory changes in branches of the brachial plexus. Deep seated pain, sharp or dull, either in the thorax or the abdomen occurs with invasion of the serous membranes.

Pain in cancer of the breast most frequently due to skeletal metastases. However, in no other tissue or organ does breast carcinoma give rise to pain of such wide-spread distribution and in such widely varying forms, from the mildest to the severest, from the dullest to the most acute, excruciating and agonizing, as when it metastasizes to the skeleton. To those who have to deal with advanced cases of breast carcinoma pain due to metastatic invasion of the skeleton is one of the major clinical problems with which they are frequently confronted. This is due on the one hand to the great incidence of cancer of the breast, and on the other to the frequency of skeletal metastases in this form of malignancy, for such metastases occur in the vast majority of advanced cases of breast carcinoma.

As stated in a previous publication,[1] the frequency of skeletal invasion in carcinoma of the breast is greatly underestimated. Although a number of pathologists[2] place its incidence at about 20 per cent yet others have found it much higher: in Kaufman's[3] series it was 53.3 per cent; in Snow's[4] unselected small number of cases, it was 75 per cent. Observations and studies at the Montefiore Hospital agree with those of the latter two investigators. During the years 1913 to 1923, there were admitted to the Cancer Division of the Montefiore Hospital 67 advanced cases of breast carcinoma. Of this number 50, or 74.6 per cent, showed multiple metastatic lesions in the skeleton, demonstrated either at autopsy or on roentgenological examination.

This high incidence of skeletal invasion in cancer of the breast explains why pain at a certain stage of the evolution of this disease becomes the most important and dominant clinical symptom and problem. For metastatic invasion of the skeleton in breast carcinoma is frequently if not invariably accompanied by the most excruciating pain, torturing its victims for months and years until they finally succumb to the disease. Frequently this skeletal invasion is complicated by spontaneous or pathologic fractures of the long bones or vertebræ. To witness the agony of one of these

victims with a broken spine, a complete paraplegia, sphincteric involvement, gangrenous bedsores and with severe lancinating pain from numerous compressed, inflamed, or violently irritated nerve roots is a heart-rending sight, indeed. It must have been the pitiable sight of one of these unfortunate sufferers that made Osler[5] pen his famous lines "Morphin, more morphin and enough of morphin must be given without stint or reserve to allay the violent agony of incurable carcinoma."

However, in the beginning the pain may be so mild or evanescent that the patient pays very little heed to it. Its mildly neuralgic and fleeting, or dull and aching character is usually diagnosed by the patient herself as a cold or rheumatism and treated with home remedies, or not at all. When later the pain becomes severe enough to force the patient to seek medical consultation its underlying serious nature in the absence of local recurrence is seldom suspected by the attending physician or surgeon. Myalgia, neuralgia, rheumatism or neuritis are the usual diagnoses made and sedatives are prescribed. When these fail to relieve, baking, electrical treatment and more sedatives are liberally administered. If the pain still proves intractable a diagnosis of hysteria or neurasthenia is made and psychotherapy and massage ordered.

Nothing could be more unsuitable than massage, and yet repeatedly this practice has been carried out not only at the suggestion of the family physician but also at the recommendation of the surgical, neurological or orthopedic consultant, usually without previous roentgenologic examination to ascertain the possible presence of metastatic bone invasion, until a sudden pathologic fracture revealed the true underlying cause of the pain.

Wherein lies the explanation for this frequent failure to correctly diagnose pain due to skeletal metastases in cancer of the breast? The following were the chief reasons as we found them in our study of the literature and the cases of skeletal metastases admitted to the radium clinic and the cancer wards of the Montefiore Hospital.

1. *Insufficient Familiarity of many Physicians with the Frequency and the Clinical Manifestations of Skeletal Metastases.* This finds its ready explanation in the paucity of the literature on this phase of breast cancer, for in spite of the fact that the Roentgen ray offers ready means to ascertain the presence of skeletal metastases, such studies have been extremely meager.

2. *Absence of Local Recurrence and Visceral Metastases.* We have repeatedly observed patients with symptoms and signs of skeletal metastases for months or even years without any evidence of local recurrence or visceral metastases.

3. *Good General Health of Many Patients Even When Long-suffering from Pain Due to Skeletal Metastases.* So thoroughly imbued has the profession become with the idea that emaciation and cachexia are the invariable accompaniments of every form of

malignant disease that in the absence of local recurrence, pain from metastatic invasion of the skeleton is often ruled out if the patient presents herself in a condition of fair general health. Yet cachexia is rarely noted even in the advanced cases of breast carcinoma unless ulceration with secondary infection has set in and marked emaciation is rarely present before the final stages of the disease.

4. *Inconstant Character of the Pain in Skeletal Metastases.* Contrary to the prevailing opinion, that pain due to carcinoma is constant, persistent and progressive, pain in the early stages of skeletal metastases may be so mild, fleeting, inconstant and ephemeral that only those who have observed its further evolution will realize its full meaning.

5. *Remission, Periodicity and Recurrence of Pain in Skeletal Metastases.* "Intermittent periods of relative or complete quiescence occur in the course of many malignant tumors," Ewing[6] states in his monograph on "Neoplastic Diseases." In no other type of malignancy have we noted such frequent remissions, marked periodicity and many recurrences followed by complete local remission or cure as in skeletal metastases of cancer of the breast.

6. *The Frequent Presence of an Inflammatory Reaction Over the Site of Pain Due to Skeletal Carcinomatosis.* Although numerous pathologists, Von Recklinghausen,[7] Lanzinger,[8] Askanazy,[9] Assman,[10] Axhausen,[11] Fischer, Defoy,[12] Courvoisier,[13] Kaufman[14] and others have described the presence of an inflammatory reaction in metastatic bone malignancy due not to any complicating infection but as a tissue reaction toward the necrosis induced or undergone by the carcinomatous growth, their observations have found but scanty recognition in clinical literature. Lack of familiarity with this manifestation of carcinomatous growths has frequently resulted in the diagnosis of a benign lesion and against malignancy.

7. *Recovery of Function Due to the Subsidence of the Inflammatory Reaction, which Usually is but a Temporary and Recurring Phase.* We have repeatedly noted how a stiffened and swollen and painful shoulder, hip-joint or spine, the seat of metastatic carcinoma, completely recovered their mobility and function as the inflammatory reaction subsided even through the size of the carcinomatous lesion determined roentgenologically remained unchanged.

8. *Failure to make Repeated Roentgen ray Examinations.* We have often observed patients who complained of skeletal pain for many months with no demonstrable Roentgen ray lesions, and who later showed a destructive bone process that occasionally terminated in a pathologic fracture. Delayed Roentgen ray findings especially in metastatic invasion of the spine are a frequent source of error in diagnosis.

9. *The Presence of an Osteoplastic Type of Skeletal Metastasis.* The lesions caused by metastasizing breast carcinoma into the skeleton are not always discrete and destructive in character. In a

certain number of cases, 14 per cent according to Kaufman,[3] marked osteoplasia or osteosclerosis occurs to such a degree that the roentgenologic appearance and the slow development of the bone lesion strongly suggest a benign inflammatory process and may mislead the most expert. A case of this kind was observed by the writer and recently reported.[1]

Illustrative Cases. CASE I.—Miss M. W., aged thirty-eight years, single, on December 25, 1921, noted the presence of a painless lump the size of a small marble in the lower and outer quadrant of her left breast. The next day she consulted a surgeon who diagnosed a malignant tumor of the breast and advised an immediate mastectomy. A radical amputation of the left breast was performed on January 24, 1922, by Dr. H. Lilienthal at the Mt. Sinai Hospital. The pathologic report was adenocarcinoma of the breast with metastases to axillary lymph nodes. The postoperative course was uneventful and the patient was discharged apparently well on February 7, 1922.

On January 31, 1922, only one week after operation, she commenced to suffer from a dull localized nonradiating recurring pain in her right anterior chest in the region of the fourth and fifth ribs. The duration of the pain was from a few minutes to several hours. Occasionally the pain was very severe and the skin over the affected site felt sore to the touch. This localized pain kept recurring until the end of February, 1924, when she developed, in addition, severe pain in the left hip followed by a limp. On April 29, 1924, a Roentgen ray examination by an expert roentgenologist "did not reveal any evidence of bone involvement in the left hip and a plate of the lumbar spine did not reveal any evidence of bone destruction." However, the pain kept growing worse. On June 7, 1924, a Roentgen ray study of the lumbar spine, pelvis and femora revealed areas of rarefaction in the left transverse processes of second and third lumbar vertebræ, and multiple areas of bone absorption and rarefaction in the upper end of the left femur and the adjoining portion of the descending ramus of the ischium and the descending ramus of the pubis.

On June 8, 1924, an attempt was made by an orthopedist to apply a plaster cast to the lower spine and left hip, but had to be abandoned, for during the manipulation the patient suddenly experienced intense pain in the left hip—she had suffered a pathologic fracture of the left femur.

On June 12, 1924, she came under my care at the Van Cortlandt Hospital. A Roentgen ray study of the skeleton on June 13, 1924, revealed not only a pathologic fracture of the neck of the left femur and a moderate amount of bone destruction involving the ramus of ischium but also an area of bone destruction in the fifth rib on the right side for a distance of about 5 cm. starting at a point about 2.5 cm. from the spinous process (Figs. 1 and 2).

Comment. Immediately after convalescence from the breast amputation this patient was placed in charge of a prominent radiotherapy and cancer specialist who is thoroughly familiar with the frequent occurrence of skeletal metastases in breast carcinoma. When she began to complain of pain in her skeleton, metastasis was suspected and repeated Roentgen ray examinations were made. Yet for more than two years after the onset of pain in her right fifth rib the Roentgen ray failed to show any destruction of bone.

Case II.—E. S., a married woman, aged sixty years, was admitted to the Neurological Division of the Montefiore Hospital on April 9, 1917, with a diagnosis of transverse myelitis. For the privilege of reporting this case I am indebted to Dr. S. P. Goodhart, Director of the Neurological Service. In April, 1915, she developed pain in the right foot and knee. The pain grew progressively worse and a few months later she became bed-ridden. In April, 1916, she was admitted to a New York hospital, where after seven weeks of observation and study a diagnosis of probable Pott's disease was made. She was discharged unimproved. At this time pain in the lower spine became constant and severe and she was unable to sit up in bed. Gradually weakness of both lower extremities developed. A plaster cast applied to her spine and worn for six weeks was followed by ulceration along her dorso-lumbar region. On October 19, 1916, she was admitted to the Mt. Sinai Hospital with symptoms of paraplegia. On November 7, 1916, she was discharged with a diagnosis of transverse myelitis due probably to vertebral invasion by tumor growth with secondary cord compression.

On admission to the Montefiore Hospital, April 9, 1917, her complaints were: Pain and stiffness of the cervical spine of two weeks' duration; pain in the lower spine of more than one year duration; weakness of both lower extremities of more than one year duration, and painful and frequent urination. Physical examination showed an elderly female, emaciated and cachectic. The neck was thin but presented no abnormalities. The chest was so greatly malformed that an exact description of it was not possible. The ribs, from the second to the tenth on the left side, were flattened. No evidence of fracture, however, was noted. "*The breasts presented no abnormalities.*" In the left axilla a hard nodule the size of a pigeon's egg was felt. The left lung apex was dull on percussion, the rest of the lungs were hyperresonant. The heart sounds were feeble and somewhat accelerated. The liver extended 3 cm. below the costal margin, and the left lobe was irregular and nodular. There was a large nodule, the size of a pigeon's egg, over the left frontal bone. The spine was markedly stiffened, with marked kyphosis of the upper cervical, mid-dorsal and lumbosacral regions. Over the lumbosacral region there was a large bed-sore. Neurologic

examination by Dr. I. Abramson showed a complete transverse myelitis corresponding to the seventh dorsal segment. Roentgen ray examination on April 19, 1917 was reported as follows: "Practically the entire lumbar spine appears destroyed. Small spots of bone destruction are seen throughout the thoracic portion of the spine and the ribs, as far as the latter appear on the spine plates. The upper portions of the femora, especially on the right side, show a great many spots of bone destruction." The patient died on April 30, 1917.

Autopsy revealed scirrhous carcinoma of the left breast with metastases to left axillary lymph nodes. With the exception of a few small discrete nodules in the lungs and liver, the chief sites of invasion of the metastatic carcinoma were in the skeleton proven microscopically (Fig. 3). The following is an extract from the autopsy protocol: "The spine in general is much more brittle and porous than normal. In places there is complete erosion of the lateral processes with protrusion of fleshy, gray-white tissue into the surrounding muscle. In the thoracic portion of the cord there is no enlargement of any portion of the vertebræ. In the lumbar portion, however, the lateral processes and spines of the second, third, fourth and fifth lumbar vertebræ are markedly enlarged and in places the bone is completely eroded by fleshy, dull-gray tissue. This is seen invading muscle in the vicinity. The swelling of the four vertebræ is very striking. In places the intervertebral discs are greatly thickened, in places greatly thinned. There are areas of calcification in all. The spine sawed in two presents a striking picture (Fig. 4*a*). The bodies of the third and fourth lumbar vertebræ are completely replaced by fleshy, dull-gray tissue with here and there injected areas. The bodies of the second lumbar and first sacral vertebræ are almost completely replaced by similar tumor tissue. The bodies of the sixth, seventh, ninth and tenth dorsal vertebræ are almost completely replaced by tumor tissue which extends to the sacroiliac joint on the right side. The replacement is so striking in the second third and fourth lumbar vertebræ that anteriorly the bone is practically completely gone and the tumor tissue covered only by the anterior ligament. Scattered throughout the bodies of the thoracic, sacral and coccygeal vertebræ, fleshy dull-gray nodules are seen within them. The lateral processes and the spines of the upper three lumbar vertebræ are very markedly enlarged and replaced in great part by tumor tissue. The bone is everywhere thinned and in places the tumor has penetrated completely through and invades the surrounding tissue. The spinal canal is considerably stenosed in the region of the first to fifth lumbar vertebræ. The tumor tissue extends to the dura but does not penetrate this membrane although it is firmly attached to it. The dura is thickened in most places over the tumor. There appears to be marked compression of the nerves just beyond their exit through the openings in the dura."

Comment. This case gives a striking illustration of the important role which skeletal metastases may assume in carcinoma of the breast. For two years this patient was ill and suffering severely from metastatic skeletal invasion with paraplegia, and yet at no time were there any clinically demonstrable signs of primary carcinoma of the left breast. Even at necropsy no gross evidence of breast malignancy was detected. Only the microscope yielded the convincing proof that the carcinomatous growth was primary in the breast. It is interesting to note that with extensive invasion of the lower spine by metastatic carcinoma, the lungs and liver were the seat of only a few tiny nodules, and the rest of the viscera were free from any gross signs of metastases. Even more interesting is the presence of marked new bone production in the lumbar and sacral vertebræ in a case that showed such extensive bone destruction in the rest of the skeleton. This attempt at new bone production or healing shows, as Handley[15] has so emphasized, Nature's method of local cure of carcinoma even in the most severe cases.

Case III.—Mrs. E. A., aged forty-two years, was first seen in consultation on May 25, 1924. In the spring of 1919, she suffered a contusion of her right breast which resulted in recurring bleeding from the right nipple for a week. She felt perfectly well for the next three years. In the spring of 1922, three years after the bleeding from the right nipple had occurred and subsided she commenced to have occasional darting pains across both upper scapular regions, lasting only a few minutes, recurring at intervals of a few months, and causing the patient very little anxiety. In September, 1922, she noted the presence of a painless diffuse induration in the lower and outer quadrant of the right breast. Slowly but progressively the mass in the right breast increased in size, and early in 1923, retraction of the nipple was noted. Her general health, however, remained excellent and she considered herself in no need to consult a physician. In April, 1923, she was seized with an unusually severe attack of lancinating pain over the upper scapular and posterior shoulder regions, and although the pain was not accompanied by any constitutional symptoms, it was severe enough to confine her to bed for several days. A physician who was consulted for the pain was not informed of the presence of the growing mass in the right breast. A diagnosis of "neuritis" was made and medication prescribed. Within four days the severe pain subsided although complete disappearance of pain and soreness did not take place until three or four weeks later. In July, 1923, a recurring attack of severe lancinating pain in the upper scapular and both posterior shoulder regions made her again consult her physician. When on physical examination the breast lesion was discovered, a mastectomy was urged. A radical amputation of the right breast for carcinoma was performed in September, 1923.

Following the operation, the pain in the shoulders and scapular regions kept recurring and in January, 1924, spread to the cervical and dorsal spine. In the shoulders especially the pain was excruciating. Having failed to relieve her of pain by baking, massage, sedatives and alcoholic injections for supposed neuritis the attending physician referred her to a neurologist. After a complete examination the neurologist failed to find any objective signs of disease and made a diagnosis of neurosis and recommended suggestion, electrical treatment and massage. These measures were scrupulously carried out until March 10, when suddenly without any premonitory symptoms and without any greater trauma than merely chewing her food she suffered a spontaneous fracture of the lower jaw. Two days later, on arising in the morning she found her left upper extremity completely paralyzed but not painful. Sphincteric involvement was evidenced by inability to void spontaneously and by obstinate constipation. A month later, complete paralysis of both lower extremities developed and in addition her right upper extremity became paretic. In spite of this extensive paralysis she experienced very severe pain along her entire spine with lateral radiation. In addition a complicating cystitis and a bed-sore combined to make her condition a miserable one indeed. At this time there appeared evidence of ponto-bulbar invasion: she began to have attacks of salivation with accumulation of secretions in her throat and lungs reaching at times the degree of a transient pulmonary edema. She died on June 2, 1924.

A postmortem roentgenologic examination of her entire skeleton revealed metastases in her right lower jaw and cervical and dorsal spine. The bodies of the sixth and seventh cervical vertebræ showed marked destruction. There was a pathologic fracture of the body of sixth cervical vertebra (Fig. 5). Small areas of bone destruction were also present in the bodies of the first, second and third dorsal vertebræ (Fig. 5). The rest of the skeleton was negative, and the lungs were normal.

Comment. This case presents in a striking manner the character and behavior of pain in the average case of breast carcinoma when its metastasizes to the spine. Yet her attending physicians had ruled out metastatic bone malignancy and diagnosed "neurosis" because "twenty-two months after she had been suffering from repeated attacks of very severe radiating pain in her cervical and dorsal spine she showed no atrophy of muscles; no sensory changes; no reflex changes; no tenderness over the spine; no rigidity of the spine, and was too readily relieved of pain by the oral administration of morphine." That these reasons were fallacious was proved by subsequent events. Only two months after a diagnosis of neurosis had been made the metastases in the cervical spine had progressed so far to cause a fracture of the sixth cervical vertebra with tetraplegia and death. The error lay in their considering only the

FIG. 1.—Pathologic fracture of neck of left femur, with slight upward displacement of the shaft and a moderate amount of bone destruction involving the ramus of ischium.

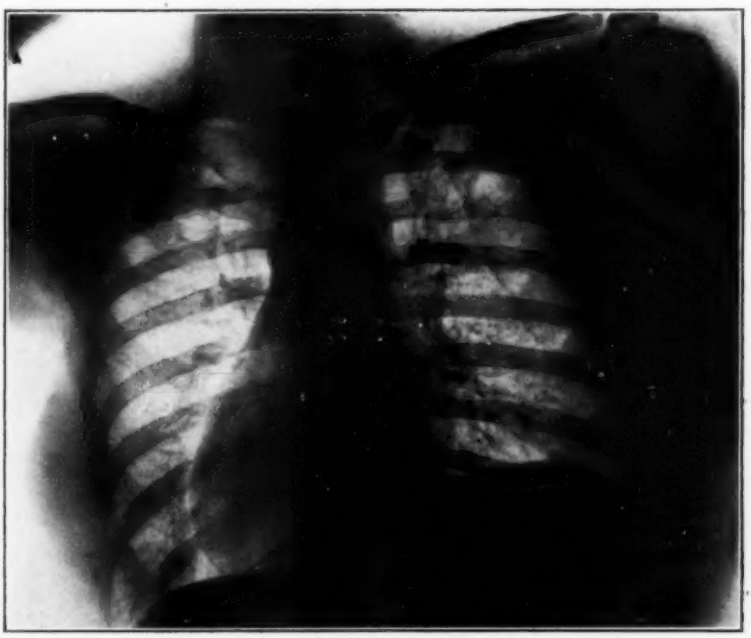

FIG. 2.—An area of bone destruction in the right fifth rib, from a primary carcinoma of the breast.

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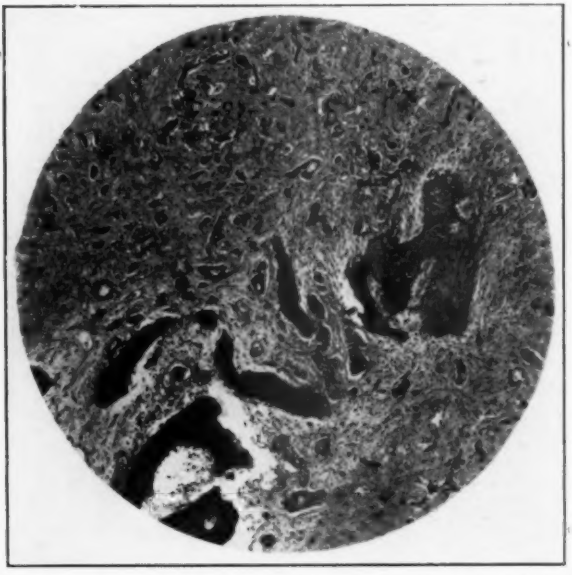

FIG. 3.—Metastases of carcinoma into a vertebra, from a primary scirrhous carcinoma of the breast.

FIG. 4*a*.—Photograph of sagittal section of lower spine, showing extensive metastases in vertebrae.

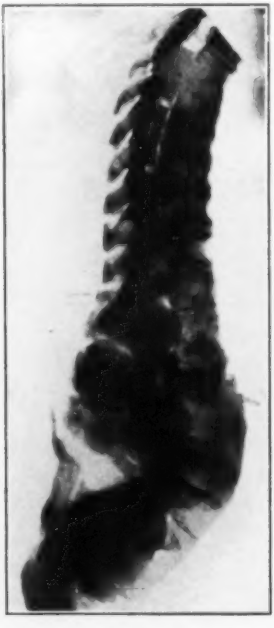

FIG. 4*b*.—Roentgenogram of sagittal section of lower spine, showing numerous areas of bone destruction and bone production.

FIG. 5.—Pathologic fracture of the body of the sixth cervical vertebra. Small areas of bone destruction in first, second and third dorsal vertebræ.

FIG. 6.—Metastatic carcinoma of skull. Marked new bone production.

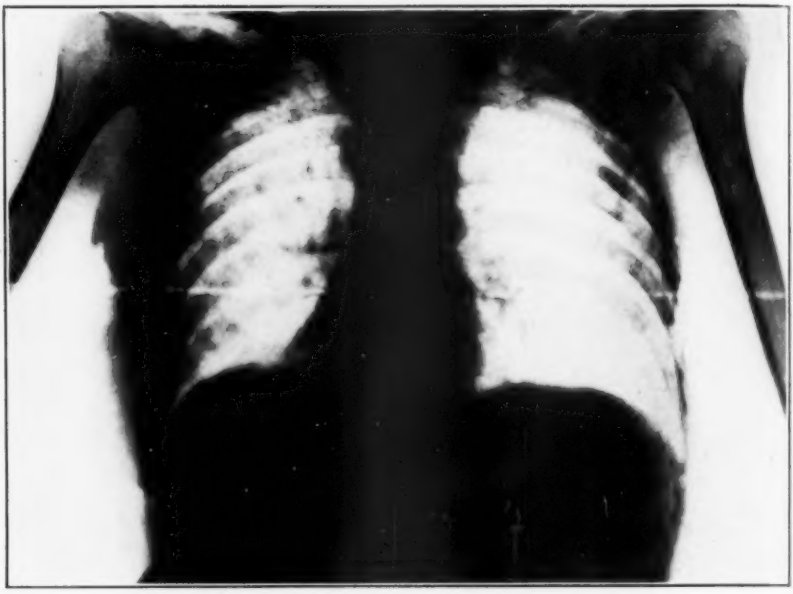

FIG. 7.—Metastatic carcinoma in both humeri and in ribs.

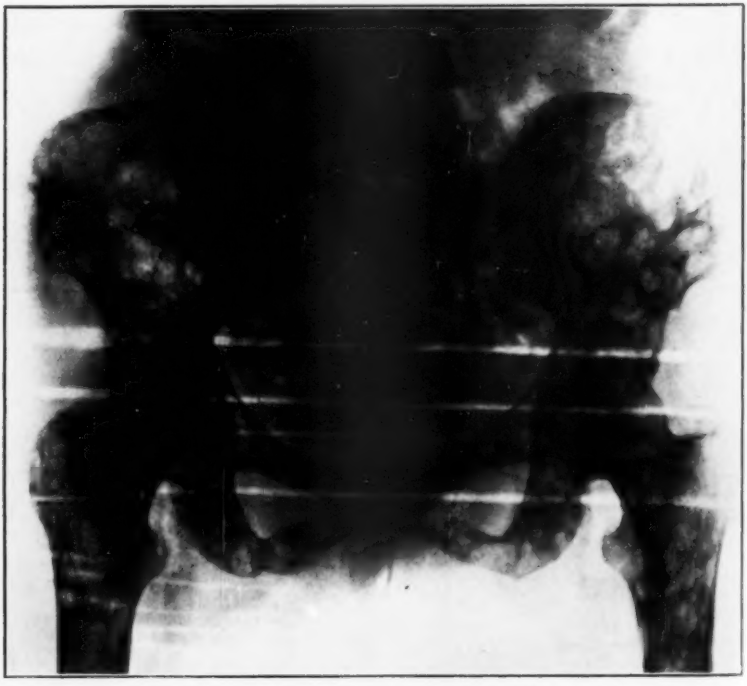

FIG. 8.—Multiple areas of bone destruction in pelvis and femora secondary to carcinoma of the breast.

FIG. 9.—Right shoulder of Case V on June 30, 1924, perfectly clear from metastases. Compare with Fig. 8. Roentgen ray taken, May 1, 1923.

FIG. 10.—Marked improvement of pelvis and femora following high voltage Roentgen-ray treatment. Compare with Fig. 8. Roentgen ray taken, May 1, 1923.

late compression phenomena of malignant growths and overlooking the role and the frequency of inflammatory reaction which may be but a transient although recurring phenomenon in the evolution of a carcinomatous growth.

Treatment. A discussion of therapy of skeletal metastases of breast cancer may appear fruitless to many. However, in bone metastases as in perhaps no other form of malignancy have we noted that tendency to local regression or cure, which Handley[18] insists occurs to some degree in every case of carcinoma, and is the more marked the more effective the local and general immunity of the patient toward carcinoma.

Clinically a number of observers[16, 21] have reported favorable results from radiotherapy in metastatic bone carcinoma, not only in the early stages but also in the advanced cases with marked bone destruction. In a recent communication Jenkinson[19] states that "in the treatment of spinal metastases, in some of the cases showing definite cord lesions, we have noted great improvement. These cases are alive after three years and are comparatively free from pain and are able to walk with no assistance . . . Results in some of our cases of spinal metastases have verged on the spectacular, especially those showing paralysis. To see a patient, bed ridden and completely paralyzed from the waist down with no control of the urine or bowels, get up and walk after a course of treatment is, to say the least, gratifying." Similar experiences are reported by Kelly and Fricke:[21] "Metastases to the spine are often helped in a remarkable and unexpected manner by heavy treatments with radium which serve to alleviate the pain and often enable the patient to live a year or two longer in comparative comfort. In some of the patients of this group there has even been an evident deposit of new bone with resumption by the patients of the normal relations of life; almost a resurrection."

We have been fortunate to get similar results in several of our own patients and here give the histories of three cases.

CASE IV.—Reported in detail elsewhere,[1] has now been observed for an additional fourteen months. Mrs. P. aged fifty-eight years, had a right mastectomy performed for a carcinoma in 1904. Thirteen years later she began to develop metastases in the following regions: Skull (Fig. 6); cervical spine; shoulders, humeri, scapulæ; superior and inferior maxillæ; ribs, and pelvis. In October, 1922, her general condition was very poor. A biopsy at that time of one of the nodes of her skull was reported by Drs. Bloodgood and Ewing as showing metastatic adenocarcinoma. Her condition was so low that her life expectancy was counted in weeks rather than in months. On February 2, 1923, after the patient had been bedridden for almost four months, and become a morphin habitué, high voltage Roentgen ray treatment was started and carried out systematically and

persistently over her skull, neck, shoulders, ribs, spine, and other involved bones, with the result that the patient was able to leave her bed in three weeks and have the morphin gradually withdrawn. Analgesia and palliation were marked. On February 26, 1925, more than two years after Roentgen ray treatment was instituted the patient was still alive and in a more comfortable condition than before the commencement of treatment. In March, 1925, she commenced to have recurring pain in various regions of her skeleton. She failed to report for any further Roentgen ray treatments. Instead, morphin in increasing doses was resorted to by her family physician. Rapid progressive deterioration set in and she died in July, 1925.

Case V.—C. T., a single woman, aged thirty-six years ,was admitted to the cancer division of the Montefiore Hospital on March 17, 1922, with a diagnosis of postoperative carcinoma of the breast with skeletal metastases. In September, 1919, three years and three months before admission, she noticed a small painless nodule, pimple-like in size, just below and to the outer region of her right breast. Gradually and painlessly the nodule increased in size extending toward the breast. At the end of a year the growth had reached the size of a small marble and was definitely located and caused a bulge in the breast. The consistency of the growth according to the patient's own words was "stony hard" but perfectly painless. It was this painlessness of the growth that barred all suspicion from her mind of the dangerous and malignant character of the lesion. In September, 1920, one year after discovery of the breast nodule, she began to suffer from severe pain over the left frontoparietal region accompanied by vertigo. The pain was constant and unremitting, boring and bursting in character. To use her own words "she felt as though her skull was being broken through." Occasionally vomiting occurred with the severe attacks of vertigo. There was frequent nausea but never any abdominal pain or colic. These attacks occurred independently of meals. For two months, until November, 1920, these symptoms continued unabated. However, she kept regularly at her work, until one day she had an unusually severe attack of vertigo and had to be taken home in a taxi. In April, 1921, she suffered an unusually severe attack of vertigo. Examination of the breast tumor led to an immediate surgical consultation, followed one week later by a radical mastectomy, performed by Dr. A. A. Berg. The pathologic report of the gross specimen was adenocarcinoma of the breast. Unfortunately no microscopic study was made. The postoperative course was uneventful. The wound healed rather slowly but closed completely in four months. During this period she felt fairly comfortable and, except for occasional slight vertigo, considered herself entirely well.

In January, 1922, with the onset of menstruation she experienced "terrific," sharp, cutting, localized pain in her sacral region, aggravated by the slightest motion. For three to four days the severe pain and disability persisted unabated, in spite of rest in bed and liberal doses of sedatives. Gradual relief then set in and she was able to leave her bed at the end of a week. In February, 1922, with the recurrence of her menstrual period the severe, lancinating pains in the lower spine reappeared in an aggravated form. Under sedatives the pain again diminished to reappear one week later in a most violent form not only at the original site but also higher up in the lumbar region. This time the pain distinctly radiated down both thighs. Within three to four days the pain disappeared entirely from the right thigh region but persisted for three to four weeks in an aggravated form over the left thigh. About the middle of the same month she experienced for one or two days very severe cutting pain in the lower dorsal region radiating band-like to the epigastrium not accompanied or followed by colic.

In March, 1922, she was admitted to the cancer division of the Montefiore Hospital. Physical examination revealed a spare, young female, presenting no edema, cyanosis or dyspnea. Pallor and emaciation were moderate. There was no cachexia. Mentality and affective sphere were normal. She was bright and alert and presented no mental depression. Pulse, temperature and respiration were normal. Teeth, tongue and throat were negative. There were no enlarged supraclavicular or axillary lymph nodes. Heart, lungs and abdomen presented no abnormalities. The chest showed a healed supple scar of a radical right mastectomy operation. There was no evidence of local recurrence. There was slight tenderness on palpation and percussion over the left frontoparietal region. No bony irregularity or enlargement was detected. The spine showed slight elevation and moderate tenderness over the entire lumbosacral region. Subjectively, there was severe pain in the spine and great difficulty on turning in bed from side to side. Roentgen ray examination of skull April 11, 1922, showed a small irregular area of bone destruction in left parietal region. Roentgen ray examination of the lumbar spine March 17, 1922, showed evidence of partial destruction of the third lumbar vertebra with a distinct narrowing of the entire body, especially the left half, and a suggestion of bone destruction in the right half of the fifth lumbar vertebra. The rest of the skeleton, heart and lungs were negative.

For a period of sixteen months following her admission until June, 1923, the clinical picture was dominated chiefly by exacerbations and remissions of severe, agonizing pain in various regions of her skeleton, mitigated partially by external applications of small doses of radium and increasing doses of hypodermic medication of morphin. Her general health deteriorated rapidly; she

kept losing greatly in weight and in strength, and grew very pale and anemic. In June, 1923, she developed generalized convulsions and for twenty-four hours was in a dazed mental condition. At this time she complained of a choking in her throat which had commenced in April, 1923. In spite of hypodermic injection of morphin, 5 to 6 grs. in twenty-four hours, she was frequently moaning with pain.

A Roentgen ray study of her skeleton at this time revealed numerous metastatic areas in the skull, cervical, dorsal and lumbar spine, with partial collapse of the third lumbar and lower dorsal vertebræ and multiple areas of bone destruction in the pelvis, both femors, in the ribs, humeri, and scapulæ. (Fig. 7 and 8.) Roentgen ray examination of the chest June 20, 1923, showed the left diaphragm to be elevated, extending upward as far as the ninth rib posteriorly. The diaphragmatic edge was irregular and there was apparently some infiltration in the lung just above it

Her condition looked critical. As a last resort to allay the violent pain in the cervical spine, and perhaps prevent a possible fracture of a cervical vertebra, deep Roentgen ray therapy was decided upon and carried out at first over the cervical spine and then over the rest of the skeleton. The technique used was: Voltage, 200,000; filtration, Cu. ½ mm., Al. 1 mm.; target distance, 50 cm.; milliamperès, 4; S. E. D. seventy-eight minutes, usually given in forty-five minutes treatments at intervals of three to four days. The first treatment was given on June 27, 1923, the second on July 2, 1923.

Following the second treatment there was a marked diminution of pain in the cervical spine. The improvement in symptoms was rapid and striking. The hypodermic injection of morphin was gradually diminished and in the early part of August, 1923, was entirely withdrawn. Coincidently with the relief from pain her general health and strength improved, and at the end of August, 1923, after a bed ridden state of twenty-two months, she was able to leave her bed and walk across the room. Those of us who saw her in a moribund condition with a skeleton riddled with metastases and undoubted evidence of cerebral irritation were agreeably surprised at such a remarkable improvement.

A Roentgen ray study of her skeleton revealed the cause of the improvement. In addition to the actual diminution in the number of metastases, new bone formation had occurred in numerous areas. This became most marked in May and June, 1924. On May 20, 1924, the roentgenologist reported: "Examination of dorsal and lumbar spine shows a decided improvement in the pathologic process in the vertebræ, especially in lower spine. Marked improvement of pelvis and upper femora (Fig. 10). Skull: reveals a marked decrease in the size and number of the metastases." Roentgen ray examination of the shoulders June 30, 1924, disclosed a marked improvement in the pathologic process, so much so, that

there was hardly a trace left of the former areas of bone destruction (Fig. 9.) Roentgen ray examination of the chest August 26, 1924, failed to show any evidence of metastases in the lung parenchyma.

The improvement continued until the end of 1924, when recurrence of pain in clavicles, neck and skull was noted. Unfortunately she left the Montefiore Hospital on December 1, 1924. Follow-up investigation elicited from the family the statement that the patient commenced to go down hill in the early part of 1925. In March, 1925, she was admitted to Bellevue Hospital where she died the same month. No autopsy was obtained.

Comment. To those who look pessimistically upon the cancer problem this case will be counted as merely one more failure added to the long list of innumerable cancer victims. To those, however, who have carefully studied the clinical course of this patient and the changes in the skeleton, a new hope must arise. For those extensive osteoplastic changes in the skeleton unmistakably indicate that the human body is not completely helpless in its struggle even against the most advanced and malignant types of carcinoma. How much the high voltage Roentgen ray treatment has been responsible for this improvement we cannot tell but that it contributed to this result we do not doubt.

Case VI.—Mrs. S. S., aged forty-five years, noted in June, 1923, the presence of a lump the size of a Lima bean in her left breast. The lump grew progressively larger and in April, 1923, was about 3 cm. in diameter. Operation was advised but refused. In August, 1923, she experienced "terrific" pain and soreness over the left lower ribs which lasted for a few months. In February, 1924, similar pain was experienced over the occipital bone on the left and over the upper cervical spine. For two to three weeks her neck was stiff and painful. A radical mastectomy for cancer of the left breast was performed on April 4, 1924, at Jefferson Hospital, Philadelphia. The pathologic diagnosis was carcinoma simplex. Axillary lymph nodes did not show any evidence of metastases.

When seen in consultation for the first time on August 15, 1924, she complained of pain in the left occiput, and entire cervical and upper dorsal spine, radiating, lightning-like, down both arms. On the left side it was reflected as far down as the elbow and on the right as far as the wrist. On physical examination no local recurrence and no evidence of metastases was found. Roentgen ray examination failed to show metastases either in the skeleton or the lungs. Guided however by our past experience we diagnosed probable carcinomatous bone metastases and decided not to wait for roentgenologically demonstrable signs of bone invasion and proceeded to treat her systematically with high voltage Roentgen rays over her skull, neck, spine and chest. The technique used was the same as that in the former cases. Instead of giving her a full

dose in one sitting we gave her forty-five minutes at each of two sittings at intervals of four to five days.

Her condition today, February 8, 1926, is excellent. She gained several pounds and her present weight is 152 pounds, the best weight she ever had. Roentgenologically to date there are only two tiny suspicious areas of bone absorption in her left pubic bone for which she is receiving treatment at present.

Conclusions. Extramammary pain in breast cancer most frequently spells cancerous skeletal metastases. Whenever a patient with breast cancer preoperatively or postoperatively, with or without local recurrence, with or without demonstrable visceral metastases, complains of pain for which no adequate or obvious benign cause can be found, one must think of skeletal metastases.

To attribute such pain to myalgia, neuralgia, rheumatism, neurasthenia or hysteria, even though no objective physical signs of malignancy are present to account for the pain, is exceedingly hazardous. Frequent and repeated roentgenologic examination of the skeleton for bone metastases should be carried out. These observations are to be continued not with a spirit resigned to failure or with pernicious methods of inunction and massage, but with intensive radiotherapy, persistently, repeatedly, and regularly administered by a competent radiotherapist.

This irradiation treatment may perhaps defer a positive diagnosis for a long, or, let us hope, an indefinite period of time. It is better, however, to have a diagnosis remain hanging in the balance than to have a life destroyed in the agony of hopelessly advanced bone malignancy.

As a corollary to the above, prophylactic postoperative radiation in breast carcinoma ought to include not only the breast region, but a judicious raying of the skeleton with special reference to the most frequent sites of bone invasion.

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SOME NOTES ON CANCER.

III.—On Cancer Proper.*

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Numerous trained minds are endeavoring to penetrate into the dark recesses of the cancer mystery by means of experimental research. The writer, a clinician, imbued with the same desire, pursues a somewhat different course. His procedure of inquiring into the genesis of cancer consists in a research of the cancer literature from which he culls and analyzes and systematizes the essential results of the original investigators. In that way, and by following established facts to their logical conclusion, he strives to gain a point of vantage from which a bird's eye view might be obtained of the whole field of cancer, and escape might be found from the bewildering and, for the clinician, mostly unprofitable detail that goes with research.

For these purposes it has been found convenient to let the inquiry proceed under the headings of: (I) Cancer Inciting Factors; (II) Precancerous State; (III) Cancer Proper—Malignancy.

The term "cancer" is being used throughout to indicate invasive, metastasizing neoplasms in general; the term "precancerous state," to indicate a morbid tissue condition of cancerous potentialities.†

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† The term "precancerous state" is not, as frequently stated, of recent invention, but occurs at least as early as 1847 (Virchow, **1**, p. 126).

Seemingly, there can be no cancer without a preceding precancerous state, and no precancerous state without a previous injury to the tissue by a cancer-inciting factor. These observations have found frequent expression.

1. As regards the preceding lesion, for instance, v. Hansemann[2] (p. 204): "Malignant tumors do not arise where the tissue is normal, but where it has undergone pathologic changes." Bloodgood:[3] "Cancer never begins in a healthy spot." Delbet[4] (p. 75): "Nobody ever saw a cancer arise in a scar healed *per primam*." W. J. Mayo[5] (p. 681): "No one has yet seen a cancer of the skin or visible mucous membrane of the body which was not preceded by some form of chronic irritation. Investigation of the inner surfaces of the body reveals the same conditions always preceding cancer."

2. As regards the conception of cancer as a series of processes, for instance, Virchow[6] (p. 73): "A tumor should not be looked upon as something complete and endowed with permanent attributes, but rather as something at every moment in process of development." Ewing:[7] "We must consider carcinoma not as a fully developed disease, but as a process which takes time and passes through stages of evolution."

3. As regards the whole course, for instance, Gebele:[8] "First injury, next inflammation and repair, next cancer." Ménétrier[9] (p. 154): "The morbid process called cancer consists of a series of stages: preparatory, inflammatory, hyperplastic, neoplastic, steps in an evolution as the final culmination of which appears cancer proper which on its part has further steps in the degree of virulence of its malignancy."

We recognize then as typical of the cancerous process a certain ever-recurring sequence of stages of development in the series of tissue changes which lead from health to malignancy: to start with, the impact upon healthy tissue of any one of the numerous cancer-inciting factors; next, as the aftermath of the injury done by the impact, the onset in the tissue of morbid changes, with the possibility of their eventuating in a series of evolutionary stages from every one of which progress of the process may take place to the next stage in the direction of malignancy. But observations show that during every one of these stages the process may also come to a halt (v. Hansemann,[2] p. 165: "In probably the majority of tumors periods of growth alternate with periods of rest"), or that it may be derailed altogether and that retrogression may occur in the direction toward healing. Clowes[10] (p. 1549): "It is probable that a very large number of spontaneous recoveries occur previous to the time at which the tumor has reached such dimensions as to be readily recognizable."

This period of uncertain changes is the precancerous state. It is not only a link which connects with malignancy the effect of the

initiatory injury, but it is at the same time a zone of hesitation and doubtful developments either way, which separates the release of the process induced by the cancer-inciting factor from the terminal malignant state.

The cancer-inciting factors and the precancerous state have been dealt with in a general way in my two previous papers under the same caption.[49] It remains now to take up as broadly and without, for the present, going into detail, the third topic—Cancer Proper.

We inquire: How does cancer be fitted into the picture that modern medicine has evolved to encompass all the ills that occur in the human organism? For, that much seems certain, if the cancer problem is ever to be solved so as to stay solved, that cancer must be removed from the pedestal of exceptionalism and unapproachableness from which it frowns down upon us, that it must be stripped of the right to the awe with which it is regarded at present, and that it must be made amenable, if possible, to ordinary medical conceptions.

That object, it seems, will have been achieved when cancer shall have been demonstrated to be like "all other vital phenomena, a reaction of the living substance to environmental stimuli" (Conklin,[11] p. 540), and to be not only "a" reaction, but a necessary, an inevitable, a lawful reaction thereto. Virchow[1] (p. 230) said in 1847: ". . . if somebody gets a tumor, the occurrence is an accident . . . by which is induced a series of phenomena, the visible result of which is the tumor. Research work, therefore, can have no other task, than to find out all about the accident and about the laws which govern the course of the sequelæ of the accident." His contemporary, Spiess[12] (p. 313) had this to say with reference to the laws: "All life . . . is the product of two factors, one extrinsic and one intrinsic. It is evident that the extrinsic factor, the cosmic influence upon the organism, can be governed only by physical and by chemical laws, for there are no other laws in Nature."

Accordingly the goal of these present studies should evidently be: (1) To show what environmental stimuli are capable of inducing the changes of the tissue observed in cancer; (2) to show how the normal tissue cells react to such stimuli; (3) to show how the reaction turns a normal tissue cell into a cancer cell; (4) to show how a cell thus changed continues to be a cancer cell; (5) to show how all this can take place within the known physical and chemical laws of Nature.

It is a formidable program and would be quite beyond the capacity of the writer to cope with, but for the literature and facts found therein that bear on these questions. It will be his aim to weld such facts, scattered far and wide, into a unit, remembering constantly that it is intended, as stated above, to demonstrate cancer as not outside of, but within the compass of ordinary medical conceptions.

Let us first have a look at these conceptions: "Omne vivum ex ovo," taught Harvey[13] in the seventeenth century, or as Weigert[14] (p. 78) quotes it: "omne vivum ex vivo." Two hundred years later, in 1855, Virchow[15] (p. 23) inaugurated a new era in medicine, when he enunciated the formula "Omnis cellula e cellula;" "cells arise only by division of preëxisting cells" (Wilson,[16] p. 5). Strassburger[17] (p. 312) modified Virchow's formula to read: "Omnis nucleus e nucleo," and Bard[18] put on the final touch by completing it to: "Omnis cellula e cellula ejusdem generis."

These observations are the solid rock upon which, as foundation, the lofty structure of present-day pathology has been erected. Thus far no room has been found in the edifice for cancer. The reason becomes apparent, when we consider the reaction of cells to a rate of stimulation exceeding their physiologic tolerance. "No morbidity causing irritation," says Virchow[19] (p. 6) "is capable of producing in the organism processes of life which in the essentials of their nature differ from those normally present." Martius[20] (p. 482): "Disease can elicit from a cell only that which is potentially preformed within it." But cancer does not seem to bend to this rule. In cancer we are apparently faced with the phenomenon of the manifestation in enfeebled, degenerating cells of powers of growth greater by far than those possessed by the unimpaired normal cells from which they descend.

It is generally accepted that cancer cells are subnormal in various particulars. Williams[21] (p. 405): "Cancer cells . . . are soon overtaken and destroyed by fatty, caseous, mucoid, hyaline and other degenerative changes . . ." Rindfleisch[22] (p. 134): "Every genuine tumor is, to start with, a local degenerative process of growth." Waldeyer[23] (p. 154): "A primary carcinoma is more fittingly described not as a tumor, but as a cancerous degeneration of the organ in question." Ewing[24] (p. 60): "Oertel's theory that tumor growth is a form of cellular degeneration . . . is a valuable working hypothesis." Yet we seem to observe in these degenerated cells, the moment malignancy has become an established fact, an extraordinary increase of vitality, a rejuvenescence, as it were, an access of power for unlimited active performance, a sudden change from restrained to unrestrained, from governed to lawless destructive growth; or rather, we call this apparently increased vitality malignancy. "Malignancy is to be attributed entirely to the capacity of the cell for unlimited growth . . . The discovery of the factors concerned in the unlimited, lawless growth of cells constitutes the main cancer problem" (Lambert,[25] p. 169). Leo Loeb[26] (p. 89): "Ultimately the cancer problem is a part of the general problem of how the proliferative power of certain cells can be increased apparently indefinitely." Roessle[27]: "At whatever point the discussion of the cancer problem is taken up, it always ends with the salient question as to the

mysterious stimulus which so changes the cells that they enter upon a course of lawless growth." "I have written of tumor growth," says MacCallum[28] (p. 1114), "separate from all the rest of pathology as a thing apart, not to be dealt with according to the laws of reaction of normal tissue." Borst[29] (p. 2): "The tumor problem is a growth problem. All other growth, such as regeneration, hypertrophy, hyperplasia, is of regulatory import; but tumor growth is from the start in opposition to the surrounding tissue and to the whole organism."

The foregoing quotations voice the currently accepted views of the different nature of "all other growth" and of "tumor growth." Cancer seems to recuire indeed a rock of its own on which to stand! Nevertheless the efforts to establish a sharp line of demarcation, separating typical from atypical cancerous growth, have failed. On the contrary stages of transition have been observed which seem to leave no gap between them. This fact proved so impressive that the thought of the essential similarity of all pathologic growth has at all times occupied the mind of cancer students. The father of cancer research, Johannes Müller[30] (p. 107), wrote in 1838 in his book, *On the Finer Structure and the Shapes of Malignant Tumors, (Ueber den feineren Bau und die Formen der krankhaften Geschwülste)*: "Carcinoma is not a heterologous tissue, and in its most intimate features does not differ essentially from the tissue elements of benign tumors, . . ." "heterologous" meaning, according to Virchow[30] (p. 236): "different from adjacent tissue." On the same subject Virchow[6] (p. 93) wrote in 1863: "There is no line of demarcation demonstrable between the tumor tissue and the matrix." The wide expanse between the "matrix" (that is the mother tissue from which the cancer tissue descends) and malignant tissue has been searchingly gone over in detail by a great many authors. The observations of some of them, when compiled and combined, seem to unfold an uninterrupted flowing into one another of stages of transition, all the way from cell function to cell malignancy.

Virchow[19] (p. 71): "There is a merely quantitative difference between irritation and inflammation,* the latter arising step by step from the former. Inflammatory symptoms differ from those of irritation only in magnitude and extent. Irritational phenomena . . . of functional, dynamic nature . . . such as pain, muscular contraction and relaxation, sensation, motion, secretion, etc. . . . are not always detectable by means of optical instruments or chemical analysis. When by and by they come to assume a more permanent character . . . when they become gross, material, anatomic, it is then that inflammation has set in." MacCallum[28] (p. 135): "Inflammation, cleansing of the site of

* "Inflammation" here does not mean infection.

injury and repair, commonly overlap and proceed together, inextricably mingled in the same area." Ribbert[31]: "Inflammation and regeneration connect without definable borderline." Marchand[32] (p. 256): "There is no clearly discernible line of demarcation between the processes of acute inflammation and healing." Versé[33] emphasizes his inability to separate with precision hyperplastic tissue proliferation from tumor growth. Van Heukelom[34] (p. 42) found far-reaching similarity of the behavior of connective tissue cells in inflammation and in sarcoma. Borst[29] (p. 129): "It is difficult, if not impossible, to distinguish an incipient sarcoma from the regenerative or inflammatory new growth of the connective tissue." Bier[35]: "The behavior of regenerative tissue in wound healing is quite similar to that of malignant growth." Ziegler[36] found it difficult to distinguish the cells of granulations from those of a large-celled sarcoma. Lewin[37] (p. 24): "In sarcoma it is hard to find the borderline at which the autonomous neoplasm ends and the infectious tumor begins.'7 Ewing[38] (p. 360): "Hodgkin's sarcoma . . . illustrates . . . the transformation of an infectious granuloma into a true neoplasm." Idem[24] (p. 34): "Inflammatory hyperplasia passes by insensible gradations into neoplastic growth." Ménétrier[9] (p. 44 and p. 349): "Cancer cells resemble those found in tissue undergoing acute or chronic inflammation, and it is possible to observe all the steps of gradual transition of one into the other." Ross and Cropper[39] (p. 23): "Cell proliferation of healing, the thickening and overgrowth and even benign tumors are steps in the development of malignant growth." Roessle[40] also sees in hyperplasia and benign tumors such steps. Merkens[41] believes he had traced from the healthy to the cancerous mamma an unbroken series of gradations which become distinguishable as different stages only at intervals, these intervals, however, having insensibly varying intermediate stages. Rindfleisch[22] (p. 339) found stages of transition in all pathologic growth, from the fungoid granulations of wound healing *per secundam* to the most violently proliferative, most virulently malignant sarcomatous growths. Spude[42] (p. 41) can find no difference in principle of wound healing, inflammation, hyperplasia and tumor growth. v. Hansemann[43] (p. 578): ". . . the distinguishing of benign and malignant tumors is postulated not from the biologic, but from the clinical standpoint. As a matter of fact a definite line of demarcation exists neither between benign and malignant tumors, nor between genuine tumors and inflammatory new growths." In mice Bashford[44] found it "possible to obtain a sequence of all the stages from the normal tissue through mere chronic inflammation and simple hypertrophy to adenoma and carcinoma."

Read in conjunction, the foregoing observations would seem to make out a complete case in support of the assertion that from functional cell phenomena at one end to malignancy at the other

end the demonstrable morphologic tissue changes flow into one another by insensible gradations, and that the clinically distinguished states—hypertrophy, hyperplasia, inflammatory proliferation, benign growth, malignancy—"are merely terms of convenience, nobody being able to tell where one group ends and where the other group begins" (v. Hansemann).

Led by such reflections, investigators arrived at the conclusion that, inasmuch as at least all pathologic growth seemed to be a unit, one and the same causative factor was probably underlying all of it. Bashford,[44] for instance, added the following remark to his just quoted observation: "The manner of the occurrence and combination of these changes strongly suggest their interdependence, and reference to a common cause." Borst[45] (p. 643): "The difficulty of distinguishing inflammatory from degenerative hypertrophy points most clearly to the existence of common underlying causes . . ." Herxheimer[46] (p. 40): "The simple healing of a wound, reparation, organization and inflammation proper, are merely quantitatively differing manifestations of the same reaction." The British Ministry of Health[47] (p. 100) is reported to have stated in 1923: "The liability of cancer to follow chronic irritation of many different types is remarkable and leads to the supposition that beneath them all there lies some common factor, as yet unrecognized, which is fundamental to the passage of a chronic inflammatory and noncancerous condition into one that is definitely cancerous." Luden[48] (p. 695) assumes that "The activity of one and the same chemical substance underlies normal proliferation, or growth, and abnormal proliferation, or malignancy."

The foregoing opinions picked at random from a greater number of similar ones evidence the broadly held belief, the so-to-speak intuitive feeling of those most familiar with these questions, of the unity in principle of everything pertaining to growth. Countless attempts have been made to explain away and harmonize the uncomfortable difference between restrained, or normal, and unrestrained, or socalled autonomous growth that hangs like a nightmare over cancer, each subsequent attempt only testifying to the nonsatisfying character of the preceding ones.

Summing up, we find cancer cells, currently recognized as cells of lowered vitality in a state of degeneration nevertheless commonly credited with undergoing in this process changes which either bring to the fore powers supposedly latent within them, or else endow them with powers of unlimited aggressive growth and destructiveness not evident in the normal cells from which they descend.

In spite of all such alleged divergence of cancerous and normal tissue, the factor responsible for the reputed exceptional powers of cancer cells is by many authors supposed to be the same as that which underlies all other pathologic growth, even all other growth

—certainly a most remarkable series of seemingly conflicting and almost mutually exclusive observations.

Can these contradictions be reconciled? This is the question with which we find ourselves now confronted. It will be dealt with in subsequent chapters.

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SOME NOTES ON CANCER.

IV. On Cell Division, Growth, and Growth in Cancer.*

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Nearly a hundred years have gone by since the similarity of the structural appearance, under the microscope, of vegetable and animal tissue was first noticed.† Science has traveled far in that century. From the question originally uppermost in the minds of microscopists, the question of the cells as building stones of the body, the ground has shifted to research into the building stones of the cell.§ In this field the microscope has no longer exclusive sway. New sciences have sprung up. Colloid chemistry and the physical chemistry of cells and tissues have become deep and many-sided specialties. In their application to cancer research they have opened up new vistas.

The text-books[1] on these subjects tell of great achievements, and themselves are marvels of learning. Yet, when one has done with them, one is impressed not so much with what we know about the cell at present, as with the outlook upon what we hope to know about it in the future, a state easy to comprehend. Consequently there is still much on which the text-books are consulted in vain for full information.

Among such matters is the question of growth. "When we attempt to explain the actual causes of growth," says MacCallum[2] (p. 177), "we are reduced to theories." Bradley[3] (p. 435): "The factors involved in growth and hypertrophy are so much more complicated than in hydrolysis—probably the same mechanism operating in the reverse direction—that we know little of them experimentally." Thus it happens that our inquiry, at this juncture where it must go into questions relating to growth, has to brave a flight into the more or less hypothetical, however hazardous an undertaking that appears to be from the standpoint of a clinician, and despite his ingrained disinclination to stray from the safe ground of ascertained facts. Even so the discussion is going to be kept close to the observations laid down in the literature. It is in the deductions from the same that points of view will be found which, in some respects, are at variance with the deductions of those who made the observations.

The question of growth in cancer came in for a large share of

* Received for publication, November 28, 1925.

† Dutrochet: Recherches sur la structure intime des animaux et des végétaux, Paris, 1827; quoted from Heidenhain: Plasma und Zelle, Jena, 1907.

§ "Omnis cellula e granulo."[29]

consideration in the preceding communication of this series.* We arrived there at the conclusion that the several observations and deductions on which the current conceptions of the process of cancer are based seem to be so conflicting as to be almost mutually exclusive, and we wound up by asking whether a way might not be discovered of reconciling the contradictions.

The question suggests that the problem of growth in cancer could well be formulated as consisting in the requirement of clearing up the contradictions contained in the two current deductions: (1) That normal cells undergoing cancerous degeneration should thereafter exhibit powers of proliferation greater than those noticeable in them before they degenerated; (2) that the processes of physiologic growth, pathologic growth and cancerous growth are deemed irreconcilably different and yet all due to one and the same underlying factor.

Whatever the results of an analysis of these points may turn out to be, the fact seems to stand out from them, that the discussion of the problem of growth in cancer, in order to be conclusive, should not be confined to, or based on, the phenomenon of growth in cancer alone, but should be broadened out into a consideration of all the factors pertaining to growth in general.

The starting point of such a discussion must evidently be the mutual relation of the cell and the medium in which it lives, inasmuch as nothing can be in the cell that has not first been in the medium: *e. g.*, Jacobs (in Cowdry,[1] p. 119): "The cell content in every cell must at some time have entered it from without . . . and such an intake must be constantly going on."

The common food reservoir for all the cells of an organism are the tissue fluids. That makes necessary the inquiry as to how these fluids themselves are fed and of what they are composed. Verworn[4] states: "Plants have the capacity, lacking in man, of absorbing directly from the soil the elements N, H, O, S, P, Cl, Na, Mg, K, Ca, Fe, Si, also C from the air, and of synthetizing them to form carbohydrates, fats and proteins. Man eats plants and plant products, the latter including animal tissue. In the digestive tract of man the ingesta are again split into their building stones, into the salts of phosphorus, sulphur, carbon, chlorine and into amino-acids containing nitrogen. By the blood these substances are carried to the tissue fluids. From them the individual cell absorbs what particular kind of foodstuffs it needs, when it needs them and in the quantity it needs, the mucous cell assimilating other foodstuff than the ganglion cell, the muscle cell other than the cartilage cell, the liver cell other than the brain cell." Von Möllendorf[5] (Hoeber,[1] p. 521): "The only exceptions to this rule form the substances soluble in lipoids, the access of which to the cells

* III, Am. J. Med. Sci., 1926, **171**, 535; I. J. Cancer Research, 1924, **8**, 45; II, Am. J. Med. Sc., 1925, **170**, 481.

is unrestrained." Abderhalden[1] (I., p. 503; II. p. 388): "As regards its nourishment, the cell is ordinarily safe against surprises. In the digestive tract the cleavage of the ingested complex food molecules proceeds to the point of their being divested of all specific characters. They are reduced to the comparatively small number of simple building stones of which all of them are composed. Thus the great variety of ingesta are only in the shape of these few (and always the same) materials carried to the tissue fluids. The cells are accustomed to this constancy of foodstuffs offered to them in their medium and, as a rule, complete harmony prevails between the composition of the medium and that of the cell." Handovski[6] states (p. 1317): "The functional efficiency of a cell essentially depends on its ionic and colloidal medium. . . . Constancy of temperature, constancy of oxygen supply, constancy of the composition of the medium, are essential factors in the life of the cell." Bradley[3] (p. 428): "The normal tissue cell is maintained at the reaction of the blood, or pH 7.4.* So long as its metabolic processes remain in equilibrium with its blood and lymph supply, there is no accumulation of carbon dioxide, sulphuric acid, phosphoric acid or acids of intermediary metabolism. Neutralization of these acids, further oxidation of some of them, outward diffusion of acid ions and inward diffusion of basic ions goes on at such a rate that the resultant reaction remains a constant." Rohdenburg and Krehbiel[8] (p. 434): "The physicochemical composition of the cell is somewhat of the following order: The cell may be considered as a gel, containing within it a more compact gel, the nucleus. In the denser gel calcium and sodium are present, while in the cytoplasmic gel potassium and calcium are present, the former predominating. These metals are present as phosphates, the chlorids and sulphates being present in the cell wall. Calcium, potassium and sodium are present in the fluids about the cell. Lipoid and lipoid fractions appear when the cell is either dividing or degenerating. Oxidizing and reduction processes which occur within the cell are associated, physically at least, with fatty acids. Glycogen appears only occasionally and is possibly also associated with oxidizing processes which accompany mitosis. The metals were the only elements present at all times in all tissues."

Let this brief, general sketch be sufficient for present purposes as an outline of the relations normally existing between cell and medium during periods of relative rest of the cell, the outstanding feature being that, within the limits of physiologic tolerance of variations of the medium, the contents of the cell and of the medium

* The neutral reaction is pH 7.00. Reaction above 7.00 denotes alkalinity; below 7.00, acidity. In the condition called "acidosis" the pH of the blood lie; between pH 7.40 and pH 7.00. Van Slyke[9] (p. 148): "pH 6.95 appears to be the most acid point consistent with life in man." Menten:[7] "In cancer the 'alkalosis' may rise to pH 7.80." See also Mathews,[1] p. 563.

are in equilibrium, or rather near equilibrium. For, the whole life of the cell seems to be an incessant struggle to maintain itself in a state of equilibrium with its medium. Abderhalden[1] (II. p. 97): "In the metabolism of the cell true equilibrium is never attained. The struggle for the same is life." Wells[2] (p. 33):" The constant upsetting of the equilibrium is what constitutes cell life."

We can now proceed to the consideration of disturbances of this quest for equilibrium and of the consequences thereof. There being these two factors: the cell and the medium, either one alone, or both at the same time may become the cause of a disturbance. It will be shown that such disturbances induce cell division. Hellin[9] (1906, p. 605): "Stimuli, including deficiency of nutrition, induce cell multiplication." Cell multiplication is either physiologic, *i. e.*, limited to the replacement of worn-out cells, or pathologic, *i. e.*, exceeding this limit. In both instances the cause of the division of the individual cell has been found to be "hunger." (Jickeli,[10] p. 6.)

Briefly stated, examination into the question of cell division will show, that in physiologic division it seems we are dealing with a temporarily sick cell in a healthy general medium; in pathologic division with an originally healthy cell in a primarily diseased local medium; in the unrestrained division in cancer with a diseased cell in a diseased local medium, the general medium of the organism being also abnormal.

If we turn now to physiologic cell division, we may ask with Roger Williams[11] (p. 20): "Why should growth tend in the direction of cell multiplication, rather than to the production of large unicellular aggregates?" but our answer will differ from the one he has given. The surface of the cell is in direct contact with the medium, the tissue fluids. As only by way of the surface can the mass of the cell absorb food from, and excrete waste into the medium, the ratio of surface to mass is an important factor in the life of the cell. The ratio is not a constant; it varies with the size of the cell. The larger the cell, the smaller the fraction of superficial area on which the unit of mass has to depend for its exchanges with the medium, surface and mass growing not at the same rate. [See Verworn[4] (p. 650 ff.); Hellin[9] (p. 598)]. For the proper metabolizing of the cell the ratio is the most favorable immediately after a cell division, when the body of the cell is smallest and the surface relatively largest; in other words, when the unit of mass communicates with the medium through the largest size fraction of the surface it can ever obtain. When the cell grows, the ratio decreases and the fraction becomes gradually smaller. Probably for a while the produced "excess amino-acids diffuse out into the blood and the lymph until an equilibrium is again attained" (Bradley,[3] p. 428). But the cell continuing to grow, eventually a stage will be reached when, clinically considered, because of

impeded assimilation and impeded dissimilation the cell would seem to suffer from asphyxia, under-nourishment, indigestion and constipation. Though living in a healthy medium with all the foodstuffs available to it, the cell is famished. Solely by reason of its growth it has been taken sick, and if it still continues to grow the disharmony with the medium will become aggravated and, in the end, the cell will succumb. "There is only one cure, cell division" (Legrand,[12] p. 88). "In the life of the cell governs this law: continue to live, that means, multiply, divide—or else perish" (Wyss,[13] p. 7). In other words, when the cell content no longer harmonizes with the medium, the cell faces the alternative of "die or divide." The cell divides. But while it is undergoing division it seems to be still in an enfeebled condition "Mitosis is a critical phase in the life of the cell" (Schleip,[14]). "A dose of Roentgen rays strong enough to necrotize the highly sensitive cells of lymphoid organs, leaves unimpaired the not so sensitive cells of a spindle-cell sarcoma, or a basal-membrane carcinoma, excepting if it happens to strike them in the act of mitosis. In that event the cell succumbs" (Schinz,[15]). v. Hansemann[25] (p. 10): "While dividing a cell drops every other function; it neither assimilates, nor dissimilates." Division completed, the overgrown sick cell has disappeared. Its place is taken by two smaller daughter cells with a ratio of surface to mass which insures their harmonious relation to the medium, restores their normal functioning and renders them useful members of the tissue to which they belong.

We saw in the foregoing physiologic cell division the cell undergo the changes and the medium remain unchanged. The same relative disharmony would arise, if the medium underwent the corresponding changes and the cell remained unchanged. But there would be this difference between the two cases, that, the cell changing, there is a limit set to the disturbance by the division or the death of the cell, whereas the medium changing, there is no such limitation. "If there occurs in the liquid medium a decided change of the osmotic pressure value, the cell suffers, because its shape, volume and water content, as well as the concentration within it of solved substances depend on the osmotic pressure surrounding it" (Hoeber,[1] p. 33). "Any increase of the extracellular osmotic pressure, *i. e.*, any rise in concentration of osmotically active substances in the serum, causes shrinkage of the cell through loss of water; any such decrease in concentration induces swelling. The most minute change of the osmotic serum concentration becomes measurable as difference in the size of the cell" (Schade,[1] p. 71). As always, so here too, the alternative for the cell is "die or divide." But in this instance, if it survives and divides, we are no longer dealing with physiologic, but with pathologic cell division. Let us see what likely is taking place.

Suppose a cell had just emerged from a physiologic division and

was, therefore, in the most favorable condition for a period of relative rest with proper metabolism and proper functioning. Suppose further, that at this particular moment the medium surrounding the cell, but no other part of the general medium, had, for one reason or another, suddenly become deficient in essential foodstuffs, or had become unbalanced in the proper ratio to one another of the contained salts, or for some other reason had become toxic for the cell. "From a colloid chemical point of view, the solution of one single serum salt is 'toxic' for the cell" (Schade,[1] p. 54). Suppose further, that the effect of this changed focus was not so violent as to kill the cell outright, but was mild and, though beyond the limit of physiologic tolerance, was giving the cell a chance to survive. Under these circumstances as explained the healthy cell, facing the changed local medium, divides. The two daughter cells, however, will not, as was the case in physiologic cell division, now get a chance to come to rest because of restored proper ratio of surface to mass, but, on coming into existence, the daughter cells will also be faced by the same influence that forced their mother cell to divide and they, in turn, find themselves placed before the alternative of "die or divide." "Cell proliferation and cell death are merely different degrees of cell injury." (V. Dungern and Werner,[16] p. 87.) If they survive, they must divide and so must their descendants, and this group of cells must keep on dividing until the intracellular condition approaches the extracellular condition so nearly that the influence of the focus has ceased to be for this group of cells a stimulus of division. In other words, the healthy cell from which we started and its descendants keep on proliferating until diffusion-in and diffusion-out has made the descendant cells equally as abnormal, equally as diseased as the focal medium which bathes them. At this juncture the proliferation ceases. "If medium A to which certain somatic cells are adapted becomes B, then these cells will multiply until they are in harmony with the new medium B." (Legrand,[17] p. 32 ff.) *In vitro*, "under otherwise equal conditions the proliferation of cells changes with the changes of the medium." (Erdmann,[18] p. 54.)

We have now considered, first, the case of a diseased cell facing a healthy medium and, second, the case of a healthy cell facing a diseased medium, and have found in both instances cell division probably enforced under the alternative for the cell of "die or divide." It remains now to consider the case of a diseased cell in a diseased medium.

In order to clear the ground for this question, another matter has first to be gone into as a preliminary, namely, an analysis of the term "growth." The term has been used freely, but we have not yet made sure that its meaning is unequivocal. Therefore, we now put the question: Is "growth" a definite, clean-cut term or has it perhaps more than one meaning?

For this analysis let us select a commonplace occurrence: On a tree in the spring leaves break forth from bursting buds. They "grow" and become a part of the well-ordered foliage. In the fall of the year the leaves get dry and drop off. They pile up at the foot of the tree, and, the more leaves fall down, the bigger "grows" the heap of dead leaves. Thus we find the English word "to grow," and the same holds good for its equivalents in other languages, to have two meanings, which designate: the one, physiologic growth, in which that which grows takes an active part by increasing the size of its characteristic shape through narrowly regulated metabolic processes under strict laws of Nature; the other one, growth consisting in the haphazard accumulation of disconnected, independent units into a heap of accidental configuration, wherein the part taken by the individual unit in making the heap grow, as well as the part taken by the heap itself in growing, are entirely passive. So there is active growth and there is passive growth; active growth in which that which grows, for instance a green leaf, does everything; passive growth in which that which grows, for instance a waste heap, does nothing.

When in the light of this analysis I came to look at the growth problem in cancer, it seemed to vanish into thin air. It was all so simple, it made me distrustful. The thought has been in my mind since early in 1922, but I was reluctant to make it known. Since then, as I kept on pursuing my studies of the literature on the genesis of cancer, the impression has been borne in on me, that the general atmosphere of cancer research is undergoing a change. It seems to be felt that a different orientation must be had. Pathology has joined forces with biology, chemistry and physical sciences. New methods of attack of the cancer problem are the order of the day. A yearning appears to be abroad for new leads. "It seems quite unprofitable," writes MacCallum[2] in 1920 (p. 1114), "to attempt new theories (of cancer) except on the basis of adequate new facts. Those at our disposal have been so well pondered over, that the newer theories proved to be merely the invention of new terms to express the old vague ideas." Rohdenburg[19] writes in 1925 (p. 341): "It seems opportune to present a new hypothesis of the genesis of neoplasia, since research along the lines now pursued is admittedly proving relatively sterile."

Believing this to be the present general spirit in cancer research, and thinking that perhaps a point of view may therefore prove as acceptable as a fact, I feel that I should overcome my scruples and submit what is on my mind to the scrutiny of those better versed in the intricacies of the cancer problem than I am.

There appears to me only one way open for attack on the growth problem in cancer, and that is: cutting the Gordian knot. Let us see whether that can be done with the double-edged sword of "passive" growth, and "enforced" cell-division. Tentatively we set up the following theses:

1. A cancer is not an *active* growth; not an *active*, lawless, unrestrained proliferation; not the product of inherent latent cell powers suddenly released, nor of supernormal powers mysteriously acquired, enabling previously normal cells *actively* to overwhelm adjacent tissue, *actively* to invade it, *actively* to penetrate it, *actively* to destroy it.

2. Cancer is a *passive* growth; not a tissue, but the accidental, haphazard, *passive* accumulation of disconnected unrelated, injured cells; not a self-built structure of characteristic architecture, but the portrayal of the ramifications of the preformed tissue spaces into which the cells were *passively* forced; not the revealment of latent characters and powers of the ascendants of these cells, but the sequel of their own degeneration, death and decay.

The knot has been cut, I think. The observation of Warburg,[26] that "actively growing cancer cells use no more oxygen than do resting epithelial cells" (Cori[27]) appears now in the light that they, the cancer cells, in all probability are using no more oxygen than they do, because they do not grow, because they too are resting, because probably nothing they do is active, because in whatever they do, be that multiplication, motion or accumulation, they seem to be using no energy of their own, because whatever energy they possess appears imparted to them.

In this light a carcinoma* appears now as a waste heap of jumbled-up, enfeebled epithelial cells, forced *passively* into the interspaces and channels of the connective tissue; forced into them, *passively*, because at the primary site of trouble the diseased medium apparently enforces cell division at such a rapid rate, that the previously formed cells seem to receive through the probable crowding of generations of younger cells an imparted, that is in the sense of Virchow[21] (p. 131) a *passive* motion. By this vis-a-tergo they would seem to be pushed ahead in the direction of least resistance and to be kept moving by the demand for space of the cells subsequently formed.

Hair grows that way; so do the nails: "ever new elements form at the root and push the older elements forward ahead of them" (Virchow,[21] p. 388). v. Bardeleben[22] (p. 395): "In regeneration, new cells formed at the edge of the lesion . . . are being passively pushed forward by the proliferation of the adjacent cells." MacCallum[2] (p. 1098): "Tumor cells . . . continue indefinitely to divide . . . regardless . . . of the existence of any space in which they can be lodged . . . ". Ribbert[23] (p. 93): "The epithelium proliferates into the depth, into the downwardly enlarging lymph channels of the connective tissue, that is, in the direction of least resistance." Versé[24] (p. 44): " . . . the epithelial cells changed their character *in situ* and

* A sarcoma is believed to embody the same general principles; but in its genesis it probably differs somewhat from carcinoma, as will be fully discussed in later chapters.

proliferated into wherever they found space." Idem[24] (p. 69): "The primarily cancerous epithelium did not proliferate directly into the connective tissue, but first in the direction where it found the least resistance." Lewin:[28] "In animal cancers the cells proliferate at first in the direction of least resistance."

It will now be my task to try and adduce in the subsequent communications further backing for the thesis that the above presentation should be regarded as a tenable position. This having been made plausible, there would then be no further question of a "growth problem" in cancer. A malignant tumor would thereafter appear not as an overmastering growth, but as a waste pile of dying cells. Infiltration would thereafter be no longer active invasion of helpless adjacent tissue by irresistible cancer cells, but the elbowing-out of the way of helpless cancer cells into whatever opening in the tissue offered space for a refuge. The incessant, hasty division of cancer cells would thereafter not appear as a symptom of newly aquired super-powers, or revealed latent cell powers, but as the passive adaptation of cells to a primarily changed focus, or foci, in their local medium, the alternative for the cells being immediate death, or postponement of the evil day by means of hasty divisions, the degree of haste depending on the degree of abnormality of the focal medium.

Everywhere the tables would have been turned. The incipient cancer would no longer be the aggressor, but the sufferer; the transformation of normal cells into cancer cells would no longer be a mystery, but an orderly process, a reaction, conforming like other reactions to common medical conceptions.

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SPINAL CORD TUMOR OCCURRING WITHOUT PAIN OR SENSORY CHANGE WITH A REPORT OF A CASE.

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Pain and alteration of superficial sensibility are generally held to be frequent findings in cases of spinal cord tumor. Their occurrence is so often observed that both have been included in the "syndrome" declared typical of spinal cord neoplasms. This syndrome, as described by many writers, consists of three cycles: (1) Root pains and paresthesias; (2) Brown-Séquard paralysis and (3) eventual motor and sensory paraplegia. However frequently cord tumors are observed whose clinical histories correspond to the syndrome just outlined, many are seen that deviate from the rule. This fact has been attested to on many occasions. Dana[1] writes: "Pain appears early and is a very frequent but not invariable symptom." In Oppenheim's[2] text one may read: "Root symptoms are usually the first sign of disease, and . . . neuralgic pains in the area of a certain nerve . . . are usually the first symptom . . . Recent cases show that such pains may be entirely absent . . . Sensibility may remain unaffected in the lower limbs for a considerable time." In a recent discussion of extramedullary tumors Stookey[3] states: "Pain is common, but many spinal cord tumors pass through their entire clinical course without pain. The symptom is not necessary for diagnosis." Frazier and Spiller,[4] in 1922, reported a case of cord tumor of three years' duration without pain and 3 cases that occurred without sensory changes. Sharpe[5] refers to cases occurring without pain or sensory symptoms, and reports 1 of his own in whose entire clinical course there was no pain and which caused no sensory disturbance for seventeen months following the onset of symptoms.

The absence of pain has been explained by two assumptions:

(1) Non-involvement of the sensory nerve roots at the level of the tumor and (2) destruction of the intraspinal pain tracts above the level of entrance of the roots when involved.

Explanation of the absence of sensory changes is more difficult. In those cases of spinal cord tumor that occur without disturbance of sensation the tumor is usually found in the anterior or anterolateral part of the vertebral canal, involving primarily the motor divisions of the cord. Occasionally a tumor occurring in the posterior half of the spinal canal gives rise to no alteration of sensation, but does produce marked motor disability. These cases are explained by the supposition that the tumor compresses the anterior motor part of the spinal cord against the hard, unyielding vertebral bodies with resultant abolition of motor function, but serves as a soft, pliant cushion resting behind the posterior sensory part of the cord and receiving the brunt of the intraspinal pressure, which if not absorbed by the tumor would act on the posterior half of the cord, causing sensory loss.

The following case is reported as an example of spinal cord tumor occurring with neither pain nor sensory symptoms:

Case Report. M. J., a girl, aged fifteen years, entered the department of neurology of the University Hospital on September 2, 1925, complaining of inability to walk and flexion contractures of the fingers of both hands. Her family history was negative. As a child she had had measles, but she gave no history of other infectious diseases, injuries or operations. She said that she was well until August, 1924; at that time her mother noticed that she held her left hand with fingers flexed. Soon afterward she was told by a friend that she did not walk right. Later she would stumble on walking and occasionally her knees gave way under her. She gradually became worse, and eventually was required to take to her bed. During her confinement in bed there was a month when she could not move her legs. At no time had she had pain or other subjective sensory disturbances. Vision, hearing, speech and swallowing had remained unimpaired throughout her present illness, and there had been no urinary disturbance. On examination she was found to be a fairly well-nourished girl for fifteen years. Her mentality was normal; hair, skin and nails were essentially negative. The pupils were equal and reacted promptly to light and in accommodation. Extraocular movements were normal, and there was no nystagmus. There was no paralysis of the face, jaws, tongue or soft palate. The muscles of the shoulder girdles, forearms and hands showed considerable atrophy, more marked on the left. The hands, especially the left, took the position of "claw" type when attempts were made to extend the fingers, and the grip was quite weak in both hands. Biceps jerks were present, but the triceps were not obtained. The umbilical reflex was not elicited

on either side. Both lower extremities were markedly spastic and in adductor spasm, but gave no evidence of muscle atrophy. Knee and Achilles jerks were exaggerated. There was bilateral patellar and ankle clonus. Babinski's sign was obtained on both sides. The patient was unable to rise from the examining table to a sitting position and she could not walk. There was no objective disturbance of superficial sensation, light touch, pin point, heat and cold being appreciated equally well over the face, trunk and extremities. She made a few mistakes when tested for the sense of motion and position in her toes.

The general physical examination was essentially negative. The blood pressure was 142 systolic and 80 diastolic. Urinalysis was likewise negative. Examination of the blood showed a slight secondary anemia: Hemoglobin, 70 per cent; red blood cells, 3,900,000; white blood cells, 8800. The differential count was normal. A lumbar puncture on September 21, 1925, yielded a clear, slightly yellowish fluid under normal pressure. Its cells were red blood cells. Both the globulin and albumin content were considerably increased. Reduction with Fehling's solution was normal. Blood and spinal fluid Wassermann reactions were negative. The gold-sol curve was 00001111000 and the mastic curve 222340. Two subsequent lumbar punctures showed an increase in both xanthochromia and solid content with normal cell counts. Examination of the ocular fundi in the ophthalmology department showed suspicious paling of the right optic disk. On September 22 Roentgen ray plates of the cervical, dorsal and lumbar spine were reported negative.

The patient presented no new complaints during the following month in the ward. Her temperature, pulse and respiration were normal. She had no pain. Repeated testing failed to reveal any disturbance of superficial sensibility. Occasional slight but definite nystagmus on deviation of the eyes to either side was noted. Manometric readings following lumbar puncture on October 20, 1925, gave evidence of complete subarachnoid block. Roentgen ray studies following the injection of lipiodol into the lumbar region on that date, and into the cisterna magna two days later, localized the block as extending from the sixth cervical to the third dorsal vertebra.

On October 24, 1925, an extradural endothelioma psammomatosum was successfully removed from this region following laminectomy by Dr. Max Peet. At the time of operation the tumor was found lying external to the dura. It extended from between the fifth and sixth cervical vertebræ to between the first and second thoracic vertebræ, and lay both posterior and to the left of the cord. That part of the tumor which had grown about the left margin of the cord completely surrounded three nerve roots at their points of issuance from the dura. Neither spinal roots nor cord were particularly flattened.

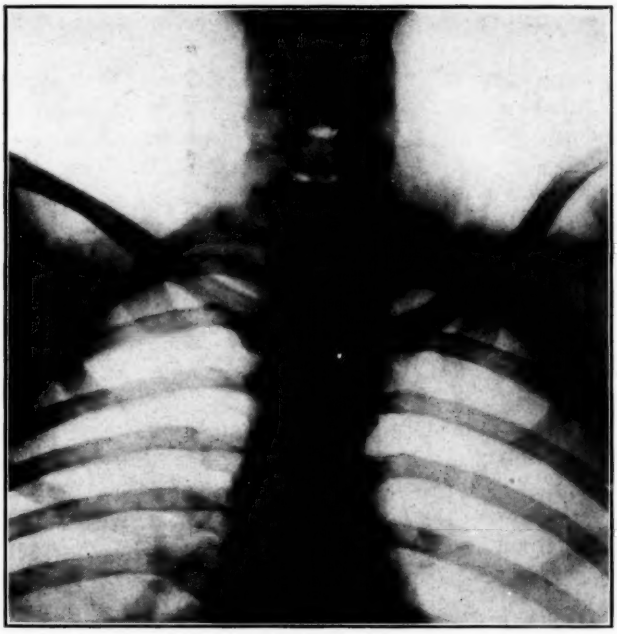

PLATE I.—Anteroposterior film taken fifteen hours after the injection of "lipiodol descendant" into the cisterna magna and sixty hours after the injection of "lipiodol ascendant" into the subarachnoid space following lumbar puncture, showing shadows cast by the oil at the upper border of the sixth cervical and the lower border of the third thoracic vertebræ.

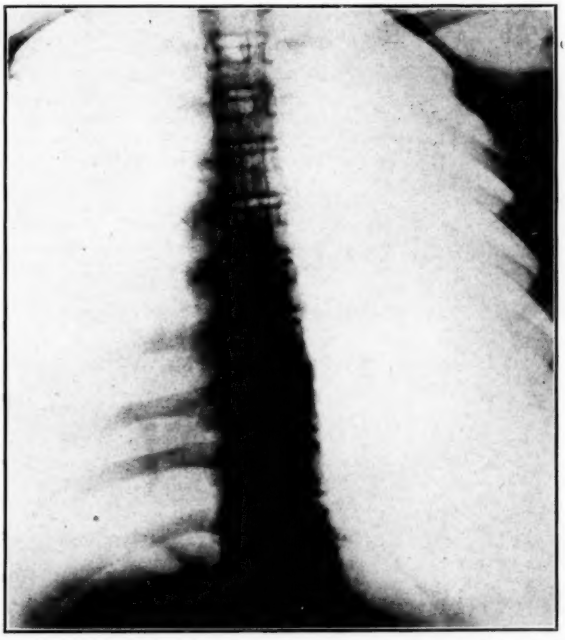

PLATE II.—Anteroposterior film taken fifteen hours after the injection of "lipiodol ascendant" into the subarachnoid space following lumbar puncture, showing the upper limit of the shadow cast by the oil at the level of the lower border of the third thoracic vertebra.

In this case the contractures of the fingers were explained by direct compression of the nerve roots, the spastic paraplegia by compression of the motor part of the cord against the vertebral bodies anteriorly. The absence of sensory symptoms at the level of the lesion was explained by the fact, now well known, that sensory fibers withstand compression far more readily than motor. Action of the tumor as a cushion behind the posterior sensory part of the cord was held to explain the lack of disturbance in sensation below the level of the lesion.

On November 24, 1925, one month following operation, the flexion contractures had disappeared almost completely from the right hand. They were still present in the left, although much less marked. The lower extremities were somewhat spastic, but not so much so as before operation. Knee and ankle jerks were still increased and bilateral ankle clonus was obtained. The Babinski sign could be elicited on either side. No disturbance of superficial sensibility could be found. The patient complained of no pain. She was able to move her toes quite readily, and at times when doing so her knees would be drawn up.

Because of the relatively short duration of her paraplegia and the early evidence of return of function it is believed that in time her recovery will be almost, if not wholly, complete.

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TYPHOID ABSCESS OF THE BREAST.

With the Report of a Case Simulating a Tumor.

By P. O. Snoke, M.D.,

Pathologic Report

By J. L. Goforth, M.D.,

PHILADELPHIA.

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Typhoid abscess of the breast is so rare that Osler places it next to last in the complications and sequelæ of the disease. The report of another case, therefore, seems desirable.

In 1895, Berg,[1] reporting 1626 cases of typhoid fever, notes that 4 cases of abscess of the breast occurred. Curschmann, writing in Nothnagel's Encyclopedia of the Practice of Medicine, states that he saw only 2 cases, both of which were in the male. Five cases were seen by Leudet[2] in twenty-five years. McCrae[3] collected the reported cases in 1903 and added 3 from the records of the Johns Hopkins Hospital. There were then 21 cases known and 16 of these had clinical records. In 1913, McCrae,[4] reporting a series of 1500 typhoid fever cases, noted mastitis as occurring in 4 cases. Madelung,[5] in 1917, found records of 30 cases, 26 of which he knew were authentic. In only 7 cases were bacteriologic studies made. In 3 a pure culture of Bacillus typhosus was found; in 2 others Staphylococcus albus was added. In the other cases typhoid bacilli were not demonstrated.

Case Report. The patient, a young colored girl, aged eighteen years, was admitted to the Philadelphia General Hospital, November 28, 1924, complaining of weakness. The family history is of no importance. She had been delivered of a child at full term December 19, 1923. The baby was nursed for three weeks and then weaned because the milk supply became inadequate. A breast binder was applied and two weeks later the patient noted several small hard lumps in her breast.

In the spring of 1924 she had a vaginal discharge. The following August she began to have lower abdominal pain which became so severe that she entered another hospital and was operated upon for pelvic inflammatory disease, on October 17, 1924. Her convalesence was normal and she was discharged November 4, 1924. One week later she lost her appetite and began to grow weaker.

Upon her admission to the hospital her temperature was 103°, pulse, 115; respirations, 22. Her history was too vague and indefinite to be of help in diagnosis or to determine when her fever began. She did not complain of her breast. The physical examination was negative except for a slight bronchitis. Rose spots were not seen. Her spleen could never be palpated. A blood count revealed hemoglobin, 8.8 gm. (or 57 per cent); white blood cells, 4500 per c.mm. with 41 per cent lymphocytes. The blood culture was positive for typhoid bacilli and the Widal test was negative. Later, during the course of the disease, the Widal test was twice repeated but was negative. The Wassermann test was negative. Her feces were cultured on three occasions for typhoid bacilli and none were found.

The course of her fever was mild. She had a slight diarrhea early in the disease and on December 8, she passed several bloody stools. On the following day a firm lump 3.5 cm. in diameter was discovered in the lower inner quadrant of the right breast. On either side of it were two smaller lumps, which were not fixed to the skin

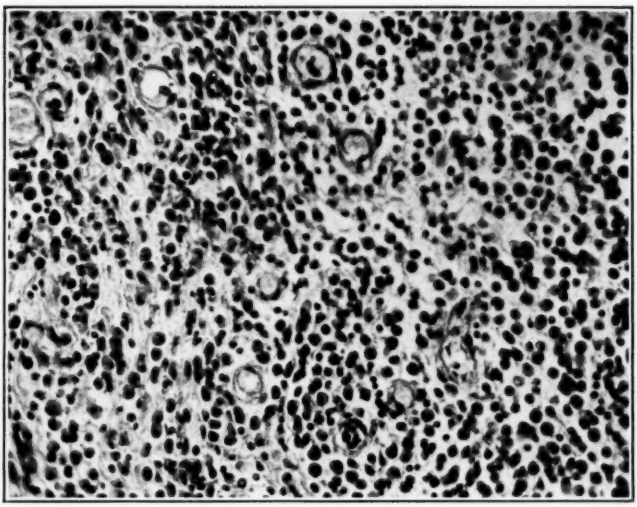

FIG. 1.—High power (400 ×) section through inner portion of abscess wall showing loose granulation tissue, heavily infiltrated with large mononuclear cells, with very few polymorphonuclears, that is, characteristic of a typhoid abscess.

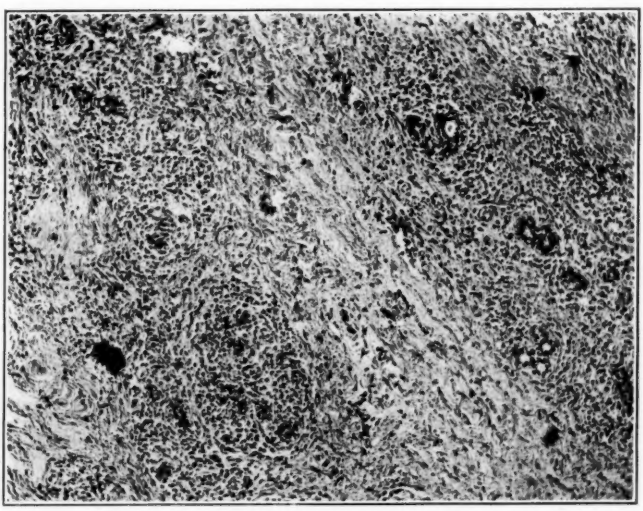

FIG. 2.—Low power (70 ×) section through outer portion of abscess wall showing chronic inflammatory changes and mononuclear cell infiltration of islands of breast glandular tissue.

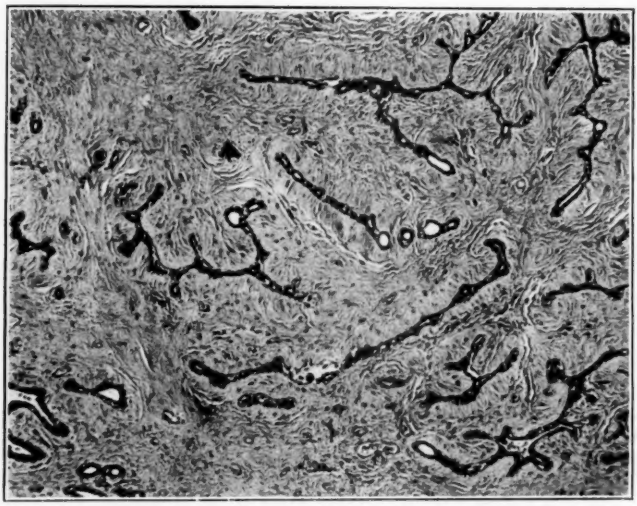

FIG. 3.—Low power (70×) section of axillary node showing periductal adenofibromata.

or chest wall. It did not fluctuate, nor was it hot or tender. The nipple was normal.

During the latter part of her convalescence, the Radiologic Staff was consulted about the mass in her breast. No definite diagnosis could be made; but the possibilities of sarcoma, carcinoma, tuberculosis and periductal adenoma were considered. She refused operation because of her recent illness and insisted upon going home to regain her strength. She was discharged January 16, 1925.

On February 2, she returned to the hospital, consenting to amputation. The mass in her breast was only one-half its former size. At one point, it had become fixed to the skin and a half inch area of fluctuation was present; elsewhere it was stony hard. A solitary subpectoral lymph node was moderately enlarged, hard and firmly attached to the fascia. The leukocytes were 7900 per c.mm. and the temperature, pulse and respiration were normal. A tentative diagnosis of tuberculosis of the breast was made.

Her breast was amputated February 24, 1925, using a transverse incision. In dissecting back the skin, a small adherent nodule was cut through and yellowish-gray, seropus exuded. This was cultured and it was later reported as a pure culture of Bacillus typhosus. The breast was excised from its underlying fascia. The nodule in the axillary fold with its adjacent fatty tissue was removed. Dakin's solution was swabbed over the raw surface of the wound. The skin was then undermined for a short distance to permit the approximation of its edges and sutured. A drainage tube was inserted through a stab wound in the posterior axillary line. The postoperative recovery was uneventful, except that when the sutures were removed on the fifth day, a small quantity of mucopus oozed from the internal angle of the wound. Cultures of it were taken and were reported as containing typhoid bacilli.

She was discharged from the hospital March 17, 1925, as cured and has been in excellent health ever since.

Pathologic Report. **Gross Description.** (Surgical Pathology No. 5829). The specimen consists of the amputated right breast and considerable fatty tissue from the axilla. A mass, roughly the size of a hen's egg, is present in the breast proper, in its lower inner quadrant. Aside from this the breast is not grossly remarkable. This mass is firm, rounded and regular, and is more or less fixed in the breast tissue; no fluctuation is demonstrable. There is no retraction or dimpling and the skin over the mass is movable. Section through the breast and mass shows a large thick-walled abscess, the cavity of which is the size of a golf ball, and the wall of which varies from 4 to 28 mm. in thickness. It is filled with orange-colored, semiliquid, purulent, putty-like material. The inner surface of the abscess wall is quite rough and is coated with a layer of this inspissated material from 1 to 4 mm. thick. A smear of the

abscess contents, stained by the Gram method, shows numerous long rod-shaped Gram-negative bacilli. The wall of the abscess is distinctly fibrous and is moderately soft. It is of uniform consistency and does not cut with unusual resistance. There are small islands of glandular tissue scattered here and there through this fibrous wall, particularly in its outer part; these show no gross changes. Grossly, the process appears to be a chronic inflammatory condition with suppuration and abscess-formation.

Five lymph node-like structures are found imbedded discretely in the axillary fat mass. They are the size of ordinary beans and are firm. On section they appear to be of dense, fibrous structure and are pearly white in color. No glandular tissue is visible. Their capsules are thick and fibrous and are everywhere intact.

Microscopic Description. Sections through the abscess wall show an ulcerating layer 2 or 3 mm. thick, in the necrotic fibrillar meshwork of which many pus cells are seen. The predominating type of pus cell is the large mononuclear cell. These occur, compared to the polymorphonuclear leukocyte, in a ratio of 4 to 1. Beneath this is a thick layer of dense, fibrous tissue, scattered through which are numerous islands of breast glandular tissue, showing chronic inflammatory changes. There is no evidence of glandular proliferation, tuberculosis or syphilis. Histologically, the picture is that of a chronic, suppurative, inflammatory process, with abscess formation.

Sections through the axillary nodules show a typical periductal fibro-adenoma picture. There is marked overgrowth of the interglandular fibrous tissue, this tending to press upon the ducts and acini, and in places, completely collapses them. There is no evidence of malignancy.

Discussion. The rarity of typhoid abscess of the breast has already been alluded to; but as typhoid fever is a bacteremia, there is no reason why the bacilli should not lodge there, as in any point of lowered resistance. Under such conditions the Bacillus typhosus tends to cause necrosis and produce pus, as more commonly seen in typhoid bone lesions. The lump noted in this patient's breast following the application of a breast binder was probably a lactation cyst or "caked breast," either of which was good culture media for the typhoid bacillus. On the other hand they may have been periductal adenomata which were first noted at that time.

The diagnosis of this lesion was difficult and unsatisfactory. At first it closely simulated a neoplasm. In the early stages it had none of the characteristics of an abscess. There was no leukocytosis. The enlarged axillary node fitted into the picture of a neoplasm as a metastatic nodule. Those who are constantly seeing neoplastic conditions are always on the watch for cases of carcinoma of the breast in young women. A number have been reported in women under twenty-one years, and sarcoma is not rare at eighteen years of age.

However, when everyone was in agreement that it was a neoplasm, fluctuation developed in the mass. The diagnosis was changed to tuberculosis of the breast, especially as the patient was a young negress slightly underweight. Tuberculosis of the breast is not as extremely rare as typhoid abscess, but on the other hand, there were no physical findings of tuberculosis in the chest.

From the initial observation of this mass in the breast until it was amputated, the most striking feature was its changeability. The patient was examined in conference three times and each time the breast presented a different appearance. It gave no indication of growth and actually decreased in size.

The pathologic and bacteriologic reports established the diagnosis of typhoid abscess of the breast. The finding of breast tissue along the anterior axillary fold is not unusual. A prolongation of the normal breast extends in this direction and aberrant portions frequently are found there. Supernumerary breasts occur frequently in this region. Periductal adenofibromata are very common and an aberrant piece of breast tissue in this site contained at least one nodule clinically. The original lumps in the breast found after the application of the breast binder may have been of a similar nature. The cysts seen in Fig. 3 contained material which might have been suitable culture media. This was a distinct and coincidental lesion which helped obscure the clinical diagnosis.

We are indebted to Dr. J. B. Carnett for the privilege of reporting this case from his service.

Summary. 1. A case is reported of proved typhoid abscess of the breast occurring in a young negress one year after lactation.

2. It was preceded by three postlactation masses; these perhaps were periductal adenofibromata, which may have afforded foci for the localization of the typhoid bacilli.

3. Enlarged masses in the axillary fold proved to be periductal adenofibromata, presumably of misplaced mammary tissue.

4. The differential diagnosis from tuberculosis or neoplasm could not be made before the breast was amputated.

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THE CALCIUM CONTENT OF THE BLOOD IN GOUT AND ARTHRITIS.

Preliminary Report.

By Philip Horowitz, M.D.,
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Calcium plays a very important role in maintaining the metabolic equilibrium and any diminution or increase in the blood is a sign of some disturbed condition. That the calcium content of the blood in normal conditions is constant and is not influenced very much by the ingestion of the calcium salts has been noted by many observers. Jansen[1] in a series of studies of calcium in man, reports that calcium given by the mouth may increase the blood calcium for a little while, but it rapidly comes back to its previous level as soon as the calcium intake is stopped. He[2] was unable to increase the level in the blood for any length of time. Denis and Minot[3] who likewise carried out a series of studies and experiments claim that it is impossible to increase the concentration in the blood to any degree if at all.

Calcium is one of the components of all cells,[4] tissue and fluids of the body. The presence of calcium is necessary to the proper functioning of the various parts of the body. The coagulation of the blood and the contractability of the heart muscle depend upon it.

The irritability of the muscle or nerve fibers is present when there is a proper concentration of the calcium in relation to the sodium content. This irritability is increased considerably when there is a decrease in the concentration of the calcium. The same applies to the peristaltic action of the colon. MacCallum was able to show that it was decreased by the calcium salts and increased by the lack of calcium salts.

Various investigators have stated that at least 1 gm. of calcium[5] is the daily requirement in man. Sherman[6] found that 0.45 gm. of calcium was the minimum amount necessary to maintain the metabolic equilibrium in man; but at least 1 gm. of calcium was required to utilize 100 gm. of protein properly, Sendler[7] agrees with Sherman and claims that the calcium balance is highly dependent on the ingestion of meat. MacCallum and Voegtlein[8] and confirmed by Salvesen,[9] found that there is a great diminution in the calcium excretion in the urine and feces of parathyroidectomized dogs. The average urinary excretion of calcium by normal adults is 0.1 to 0.4 gm. daily, expressed as calcium oxide. This is about 10 to 40 per cent of the whole excreted. The greater part is eliminated by the feces, the proportion depending on the calcium content of the food.

FIG. 1.—Case LI. Shows the upward displacement of the patella and fibrous ankylosis between patella and articular end of femur.

Comment: The above case is one of arthritis deformans with ankylosis of knees—one elbow and wrist—and has a calcium content of 12.80 which is much higher than normal.

FIG. 2.—Case LVI. Shows marked deformity of the interphalangeal joints. There is a marked hyperplasia of bony tissue and ankylosis.

Comment: This case seems to be complicated by more than one condition. There is present a gouty arthritis with a superimposed osteo-arthritis of the hypertrophic type or an arthritis deformans. While the patient is still deformed and cannot walk straight and likewise has trouble in her hands, shoulders, neck and elbows. The fact that she has responded so well to treatment has a normal calcium, places her rather in a classification of gouty arthritis.

FIG. 3.—Case XL. Radiograph of the above hands showing an osteo-arthritis of the hypertrophic type.

Comment: This case is one of an osteo-arthritis of the hypertrophic type with the formation of exostoses. The calcium is 11.70 mg. per 100 cc. of blood plasma, only slightly above normal.

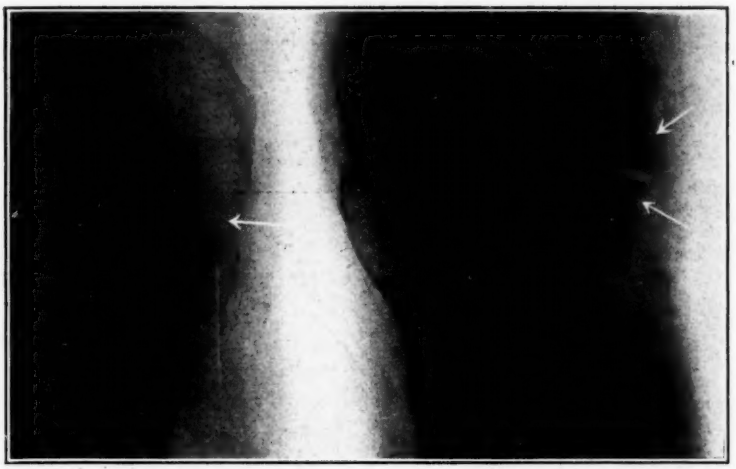

FIG. 4.—Case LXXV. Shows the same punched-out areas on external aspect of left tibia and femur. The right knee shows the presence of marked arthritis in an earlier stage before any of the punched-out areas could be formed.

Comment: This case is one of marked arthritis deformans superimposed on a gouty arthritis.

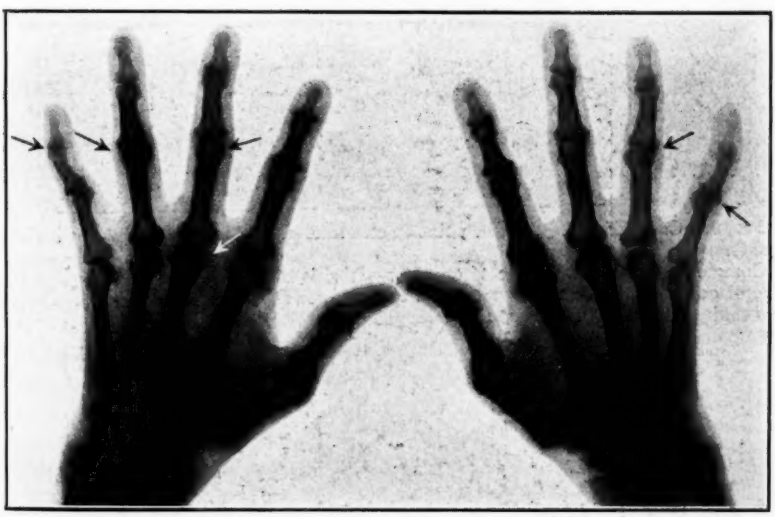

FIG. 5.—Case XXXIX. Arrows point to beginning punched out areas and formation of exostosis (gout).

Comment: This case is one of chronic gout associated with an intestinal toxemia caused by a Welch infection. The Roentgen ray shows characteristic changes of gout. The calcium content of the blood is only slightly above normal.

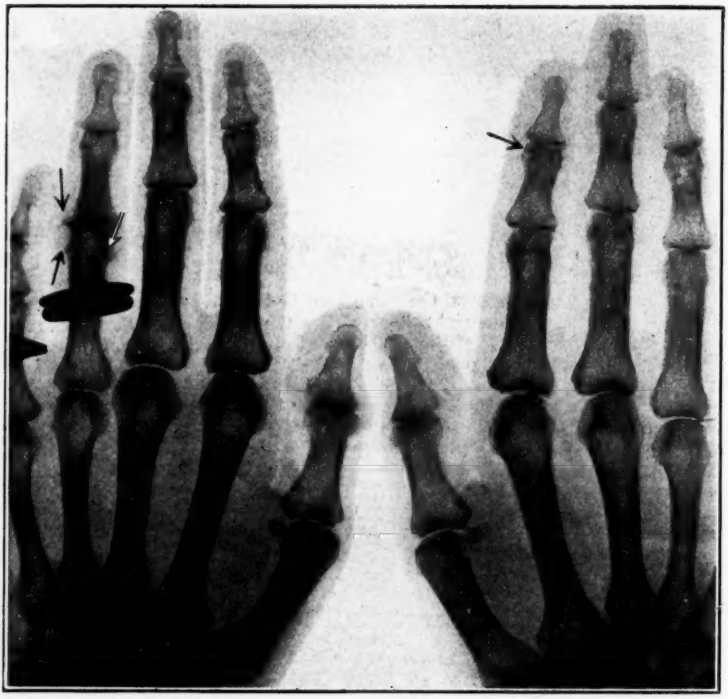

FIG. 6.—Case XLVII. Arrows point to exostosis and also to punched-out areas. (gout).

Comment: This case is one of an osteo-arthritis of the hypertrophic type, and also of gouty origin, especially marked in ring finger of left hand between proximal and mid-phalangeal joint. Blood calcium slightly above normal.

A curious phenomenon has been observed. If the calcium intake is low, the percentage of the total excretion taking place by the urine is higher or *vice versa*.

But while overfeeding or starvation may show a change in the calcium excretion in the urine or feces, the calcium content of the blood remains almost unchanged. However, the calcium content of the blood has been found to vary in certain diseased conditions. Zondak[10] found a lowering of the blood calcium in the beginning insufficiency of the kidneys. In preuremic conditions even without hydremia, the calcium was as low as 6.5 to 7 mgm. Allen[11] and Rabinowitch[12] likewise report a lowering of the blood calcium in nephritis complicated by uremia. But Allen claims that the calcium concentration is within normal limits in uncomplicated chronic nephritis. In mechanical insufficiency, however, as in tuberculosis of the kidneys the calcium was normal or slightly above normal. Hypocalcemia was found by Talbot and Denis[13] in pneumonia. Kahn[14] and Mark[15] reported that the calcium content of the blood was normal in diabetes. Rosenbloom[16] in a series of studies of calcium in gout, concluded that the metabolism of calcium and magnesium in chronic gout is normal. Coates and Raiment,[17] however, in a report on 8 cases of acute gout, found a considerable increase of the calcium concentration in the blood serum. Weil, Guilliaum and Weissman-Netter[18] likewise found an increase of the calcium in 11 cases of chronic rheumatism. Kopetsky and Almour[19] in a preliminary report on the blood calcium in undifferentiated deafness, found a low calcium in cases of otosclerosis. Mark[20] reports 3 cases of arthritis deformans that show a high calcium content of the blood. Hamilton[21] in a series of experiments on epileptic patients found the blood calcium to be normal.

All who have had any experience in the treatment of arthritis, know that there are a great number of cases that show marked symptoms such as pain, progressive disability and even the presence of a multiple arthritis, that respond readily to treatment. Whereas there is another group of cases with only slight disability and little or no pain, that progressively go on to marked deformity and chronic invalidism in spite of all that can be done for them.

It is for the purpose of differentiating cases of a gouty origin, or those brought about by an intestinal toxemia from those that are of the progressive deforming type, that this study which is merely a preliminary report, has been undertaken.

Although diet has little or no influence on the blood calcium, the blood, nevertheless, was taken before breakfast. The tests, in the cases reported, were performed by the Kramer and Tisdall[22] method, which employs only the blood plasma, and rechecked by the Clark and Collip[23] modification.

Various methods give different normal limits of the calcium

both for the plasma and whole blood. The following table shows the normal as expressed by these various methods:

TABLE I.—NORMAL BLOOD CALCIUM EXPRESSED IN MILLIGRAMS PER CENT BY VARIOUS METHODS.

Method.	Serum or plasma.	Whole blood.
Lyman[24]	...	7.6 to 11.7
Halverson, J. O. and Bergheim[25]	...	9.6 to 10.8
Cowie and Calhoun[26]	12.07	8.45
Kramer and Tisdall[22]	7.5 to 10.5	
Clark and Collip[23]	7.5 to 10.5	
Fiske[27] (Modification of Kramer and Tisdall method)	9.6 to 12.8	
DeWard[28]	10.8 to 11.6	

Complete blood chemistry was performed on the 78 following cases which complained of pain as an outstanding symptom. Eighteen of this number were diabetic. Three cases, Nos. 52, 65, 66 had a complicating severe nephritis with hydremia. Case No. 6 is a typical case of renal diabetes. Cases Nos. 16, 27, 28, 29, 34, 39, 40, 46, 51, 56, 57, 59, 64 and 75; 14 in number, are typical of, the deforming type of arthritis. While all complained of pain 32 showed an involvement of one joint to a general polyarthritis. Four cases, Nos. 13, 15, 29 and 30 have deafness as a complication, and No. 15 confirms the findings of Drs. Kopetzky and Almour.

TABLE II.—BLOOD CHEMISTRY OF DIABETICS.

Case number.	Case.	Milligrams per 100 cc. of blood.				
		Sugar.	Urea nitrogen.	Uric acid.	Creatinine.	Calcium.
1	Mr. E. H. S.	183	21	4.6	1.3	15.5
2	Mrs. Y. C.	347	16	1.3	1.2	7.2
3	Mr. J. M.	394	19	1.8	1.5	10.2
4	Mr. M. F.	160	21	1.2	1.3	8.2
5	Mrs. J. P. McG.	280	22	4.7	1.5	10.4
6	Mr. N. L.	91	18	4.0	1.4	11.4
7	Gen. W. H.	119	17	5.2	1.8	11.0
8	Mr. A. K.	188	21	4.2	1.6	10.5
9	Mr. S. W.	191	18	6.3	1.4	11.7
10	Mr. L. T.	239	21	6.5	1.7	11.9
11	Mrs. A. M.	315	14	5.3	1.5	10.5
12	Mr. W. G.	440	17	2.0	1.5	11.7
65	Mrs. F. L.	158	18	10.7	3.8	6.8
66	Mr. N. M.	186	23	8.0	1.9	7.9
68	Mrs. T. H.	137	15	1.4	1.3	12.4
70	Mr. A. R.	300	15	4.4	1.4	12.2
71	Mrs. E. D.	243	14	3.1	1.4	11.9
72	Mr. D. G.	151	19	2.2	1.2	11.2

TABLE III.—BLOOD CHEMISTRY OF CASES WITH JOINT PAINS.

Case number.	Case.	Milligrams per 100 cc. of blood.				
		Sugar.	Urea nitrogen.	Uric acid.	Creatinine.	Calcium.
13	Mrs. I.	112	18	4.2	1.5	8.9
14	Mrs. A. L.	103	20	5.7	1.1	10.1
15	Dr. V. H. P.	116	21	5.0	1.6	6.2
16	Mrs. A. V.	120	20	4.0	1.6	8.0
17	Mr. H. R.	90	24	4.7	1.6	11.6
18	Mr. J. D.	91	19	8.0	1.3	5.4
19	Mr. C. H.	104	16	3.9	1.5	10.9
20	Mr. M. A.	99	19	4.0	1.4	14.1
21	Mrs. S. D. F.	90	17	6.9	1.3	12.2
22	Mrs. F. G.	90	12	5.4	1.2	8.7
23	Mr. E. P.	116	15	4.0	1.5	11.8
24	Mr. S. A.	114	16	4.2	1.4	14.1
25	Mrs. H. J. T.	107	13	2.9	1.3	10.8
26	Mr. J. H. F.	115	15	5.8	1.5	10.2
27	Mrs. C. W.	90	14	2.8	1.2	10.9
28	Mrs. J. J. S.	89	24	2.8	1.5	16.2
29	Mrs. H. C. S.	112	14	4.3	1.3	8.1
30	Miss A. E.	130	12	12.1	1.0	9.1
31	Miss N. D.	127	22	3.2	1.4	11.1
32	Mrs. J. F.	123	19	3.8	1.5	10.7
33	Mrs. D. C.	89	18	3.3	1.5	11.3
34	Miss B. H.	116	25	4.0	1.5	11.7
35	Mrs. M. B.	131	17	2.7	1.5	10.9
36	Mr. J. W.	94	19	3.0	1.3	11.1
37	Mrs. M. O'L.	108	17	3.8	1.5	10.2
38	Mr. B. S.	122	18	3.4	1.5	10.7
39	Mrs. I. H.	117	14	4.5	1.4	11.0
40	Mrs. S. H.	117	17	5.3	1.9	11.7
41	Mrs. R. S.	81	17	6.4	1.5	10.1
42	Mr. C. E. P.	118	19	4.4	1.5	14.8
43	Mr. L. S.	110	19	4.6	1.3	11.2
44	Miss M. T. M.	71	15	7.1	1.1	11.2
45	Mr. L. E. W.	104	13	8.9	1.4	9.7
46	Mrs. S. S.	89	16	8.6	1.5	11.4
47	Mrs. C. W.	108	11	3.7	1.3	11.6
48	Mrs. B. K.	97	11	3.0	1.3	7.2
49	Mr. R. H.	70	17	4.4	1.7	11.2
50	Mr. C. F.	100	10	2.4	1.4	12.0
51	Mr. A. D.	81	12	6.0	1.1	12.8
52	Mr. J. D. C.	90	19	11.2	3.5	10.3
53	Mr. N. R.	77	15	8.0	1.3	10.6
54	Mr. D. H.	73	13	7.6	1.4	10.2
55	Miss P. H.	112	15	2.3	1.2	11.1
56	Mrs. J. D. L.	71	15	4.1	1.5	10.9
57	Mrs. M. F.	116	14	6.4	1.1	10.4
58	Mrs. I. G.	84	10	8.1	1.3	11.9
59	Mrs. R. S.	109	15	9.3	1.3	14.2
60	Miss B. P.	80	17	5.6	1.5	15.6
61	Mrs. R. J. W.	81	15	8.8	1.3	16.8
62	Mr. M. A.	130	19	5.5	1.3	11.6
63	Mr. I. J. M.	91	16	6.5	1.2	12.0
64	Mr. F. F.	94	15	3.9	1.3	9.4
67	Mrs. W. H. P.	70	11	9.0	1.3	10.5
69	Mr. M. S.	94	25	2.2	1.4	9.8
73	Mrs. E. N.	116	9	5.1	1.1	10.1
74	Mrs. T. B.	104	13	2.6	1.5	10.5
75	Mrs. M. D. F.	90	20	4.3	1.6	10.1
76	Mrs. M. B.	130	12	1.5	1.5	9.9
77	Dr. M. J. M.	98	10	3.7	1.3	9.8
78	Mrs. H. H.	70	1	3.8	1.5	10.2

A careful examination of Table II and III will disclose that only 16 out of the 78 cases reported, show a uric acid that is within normal limits; 28 have a uric acid concentration of over 5 mg.; and 14 have a concentration of over 7 mg. A further analysis demonstrated a curious phenomenon. The cases that are afflicted with the greatest amount of disability and deformity excepting Nos. 46, 51, 57 and 59 have an average uric acid concentration of only 4 mg.

TABLE IV.—BLOOD CHEMISTRY OF ARTHRITIS WITH MARKED DEFORMITY.

Case number.	Uric acid.	Calcium.
16	4.3	8.0
27	2.8	10.9
28	2.8	16.2
29	4.3	8.1
34	4.0	11.7
39	4.5	11.0
40	5.3	11.7
46	8.6	11.4
51	6.0	12.8
56	4.1	10.9
57	6.4	10.4
59	9.3	14.2
64	3.9	9.4
75	4.3	10.1

A careful study of Table IV, wherein there is an enumeration of 14 cases of arthritis with marked deformity, shows that a high calcium concentration is not always an accompaniment of arthritis associated with deformities, for it is present in only 5 cases, or 36 per cent, while in 6 cases, or 43 per cent, there is only a slight increase over normal. The only conclusion that can be reached from this analysis is that gout itself may assume a multiplicity of forms in joints, and that we cannot consider cases in which there is a marked hypercalcemia as the only true cases of arthritis deformans. Furthermore cases Nos. 1, 20, 50, 60, 61, 68 and 70 cannot be considered potential cases of arthritis deformans in whom the process has not gone on far enough to bring about real deforming arthritis, for in agreement with the findings of Coates and Raiment, they appear to be cases of acute gout.

The remaining 48 cases in whom there is a uric acid concentration of the blood of 4 mg. and over are partially gouty in character and partially due to a metabolic disturbance brought about by an intestinal toxemia for practically all have responded to treatment when the metabolic disturbance was corrected, and the intestinal toxemia removed.

The diabetic group excepting Nos. 1, 65, 66, 68 and 70 show in conformity with reports of Kahn, Mark and others, a normal or slightly above normal calcium content.

Of the 3 nephritic cases, Nos. 52, 65 and 66 only 65 and 66 showed

a fairly low calcium concentration. Case No. 52 who has since died in uremic coma showed a normal calcium of 10.30 mg. per cent.

The following reports are of characteristic cases which best demonstrate the above points.

Group I reports cases that show the greatest amount of deformity.

CASE LI.—Mr. A. D., aged thirty-nine years, native of Canada. Family and previous history negative. Present history dates back to 1914, when right knee became swollen and painful. This was followed by a general polyarthritis. The condition cleared up and for six years he was free from all pain and disability. For the past five years both knees have become involved and have gradually become so bad and ankylosed that he had to give up crutches and walk on knee pads, on his knees. Examination discloses ankylosis of both knees at right angles to the body. Right elbow is partially ankylosed and permits straightening arm up to 150 degrees; both wrists are stiff and the middle phalangeal joint of middle finger of left hand swollen.

TABLE V.—BLOOD CHEMISTRY OF CASE LI.

Tests.	Mgm. per 100 cc.
Sugar	81.37
Urea nitrogen	12.13
Uric acid	6.04
Creatinine	1.09
Calcium	12.80

CASE LVI.—Mrs. J. D. L., aged sixty-three years, native of United States. Present history dates back to 1917, when she complained of pains in both knees which cleared up readily under treatment. In 1921, pains began again involving both knees, wrists, hands and shoulders. Both knees are ankylosed at almost right angles, left wrist ankylosed and rigid and both elbows are involved and can only be straightened out to about 165 degrees. Knees are markedly swollen and cannot be straightened at all. Hands are deformed and the metacarpal-phalangeal joints are enlarged as well as some interphalangeal joints.

Under treatment this patient has discarded her crutches and is able to get about without any help and the knees have straightened to about 165 degrees. Pains, however, are present on and off, especially in shoulders and neck. The hands still show deformities. For blood chemistry, see Table II.

CASE XL.—Mrs. S. H., aged fifty-two years, native of United States.

Family History. Father died at the age of sixty-seven years from Bright's disease; mother died at the age of sixty-eight years from sarcoma.

Previous History. Excepting for the ordinary diseases of childhood, was never ill.

Present History. Dates back for a number of years. The condition began with swelling of the small joints of the fingers, which finally became deformed. She had trouble with feet and arches and the condition was so bad that she has undergone an operation to have them corrected. Knees are painful but not very bad at the present time although she cannot walk very well—the bowels do not move very well and has occasional headaches and dizziness. Examination, looks fairly well; hands badly deformed, especially the first fingers; liver palpable; heart and lungs O.K. Urine showed trace of albumin, indican 3+; uric acid less than 0.025 per cent.

CASE LXXV.—Mrs. M. D. F., aged forty-six years, native of United States.

Family History. Negative.

Previous History. Ordinary diseases of childhood and tonsillectomy seven years ago for infected tonsils.

Present History. Dates back eight years. Began with swelling and pain in one knee and gradually spread to entire body. Seems to have had an infection in right knee which was opened and drained and since then all the joints of the body became involved, feels changes in weather very much. Examination: Looks very thin and emaciated; large dark rings under eyes; skin pale; joints all over body swollen; both knees, hips and wrists are ankylosed; hip tilted downward on right side; lungs negative, heart normal in size with accentuation of second sound; jaws are somewhat rigid and she cannot open her mouth very far. She cannot sit down; rests only in a recumbent position. When she walks she slides her feet along as she cannot lift them; hemoglobin, 60 per cent; white cells, 7500; red blood cells, 3,450,000; differential normal and blood culture normal; Wassermann negative.

CASE XXXIX.—Mrs. I. B. H., aged sixty-three years, native of United States.

Family History. Father died at fifty-eight years; cardiac. Mother lived to be ninety-two years; but was rheumatic for latter half of her life.

Previous History. Excepting for some stomach disturbance and ordinary diseases of childhood; was practically well and had no serious disturbances.

Present History. Dates back three years. It began with pain and swelling in right forefinger and then spread to all the small

joints of both hands; then involved wrists, knees, ankles and feet. She sleeps poorly and is extremely nervous. There are no headaches or dizziness; the bowels move fairly well with acidophilus milk. At the present time (June, 1925) the chief complaint is pain and disability; both in hands and knees. Examination: looks fairly well; skin somewhat yellowish; eyes somewhat jaundiced; tongue clear and moist; lungs normal; heart indefinite systolic murmur which comes and goes; liver palpable. Hands and fingers are beginning to be deformed; knees swollen and bent at an angle of 135 degrees and are tender to the touch.

GROUP II.—These are cases with little or no deformity but have a normal to a high concentration.

CASE XLVII.—Mrs. C. W. W., aged fifty-four years, native of United States.

Family History. Negative.

Previous History. Ordinary diseases of childhood—anemia during early adolescence and thyroidectomy five years ago. (For Graves' Disease.)

Present History. Dates back over twenty years. The joints of fingers and both hands badly swollen and ring on ring finger of left hand could not be removed for at least eight years. In order to get some relief from pain had all sorts of treatment, and finally, as a last resort, had all her teeth and the tonsils removed. Examination: Looks very well nourished and excepting for swelling of small joints of hands and fingers and enlargment of ankles; shows nothing abnormal. Finger joints (especially the mid-phalangeal) are swollen and tender and have a bluish hue; both ankles swollen and painful and heel of right foot so painful that she finds difficulty in walking. Roentgen ray shows an osteo-arthritis of the hypertrophic type involving ring finger.

CASE LXI.—Mrs. R. J. W., aged twenty-six years, native of United States.

Family History. Negative.

Previous History. Excepting for ordinary diseases of childhood, is negative.

Present History. Dates back four years and the trouble lasted for an entire year; she had her tonsils removed and was free from pain for three years. Three months ago had a sore throat in the form of a bad pharyngitis, and all the joints in the body began to pain her again. She ran a temperature during the time she had the sore throat. She is very stiff on arising and the small joints of her right hand now bother her very much. Examination: Looks fairly well; blood pressure, 90/50. Heart and lungs negative; throat normal in appearance; all the mediocarpal joints of right hand

painful and swollen, especially that of middle finger. Radiograph of teeth show them all to be normal; blood culture negative; differential negative; urine shows 4 + indican; uric acid less than 0.025 per cent.

Comment. This case is one of acute gout and has a high blood calcium. (See Table III.)

Conclusions. From an analysis of the data obtained the following conclusions have been deduced:

1. In 5 out of 14 cases of arthritis deformans, a high blood-calcium concentration was found. In the 9 remaining cases, the calcium was within normal limits.
2. Cases of acute gout show a high calcium concentration.
3. In chronic gout the blood calcium was found to be within normal limits.
4. In a case of arthritis complicated with an otosclerosis, and in others complicated with chronic nephritis a hypocalcemia was present.
5. In agreement with other investigators, the author found that the blood calcium in diabetes was normal or slightly above normal.

In consideration of the above data, the author finds that the knowledge of the blood calcium, excepting in acute gout, whether during attack or in the interval, is of no help in distinguishing gout from arthritis.

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HYPERTROPHY, CONGENITAL, OF THE LEFT SHOULDER GIRDLE, ARM AND HAND, WITH NAEVUS AND VARICOSE VEINS.

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For the sake of description congenital hypertrophy may be divided into two groups; partial and total. Partial hypertrophy is a uniform overgrowth of a part, or parts of the body. These hypertrophies may be crossed; that is, the upper extremity, one-half of the face, or one-half of the whole head may be involved on one side of the body and the foot or toes on the opposite side. The classical example of partial congenital hypertrophy is that of Thomas Wedders' nose which is reputed to have been 7½ inches long.[28] Total congenital hemihypertrophy is a uniform overgrowth of the entire half of the body.

Anomalies of anatomical development are common, but anomalies of development in which the part or parts are developed out of proportions to the other parts are not very common.

Historical. The classical and medieval writers were zealous collectors of anomalies of all sorts. It is not easily understood why no mention is made of an anomaly which can be interpreted as one of congenital hypertrophy unless the earlier cases were mistaken for atrophy of the remainder of the body; the hypertrophied parts considered normal. The first case of congenital hypertrophy was reported by Wagner,[27] in Germany, in 1839.

Since Wagner's report the rarity of the anomaly is best demonstrated by the slow accumulation of case reports. In 1889, Osler[21] found only 12 cases reported in the entire literature. Leblanc,[17] in 1897, for his thesis for the Doctorate of Medicine in Paris, collected 78 cases. Gessell,[13] in 1921, collected 40 cases of total congenital hemihypertrophy and added 1 case himself. Gessell did not attempt, as did Osler and Leblanc, to collect all of the cases reported as he was principally interested in the total hemihypertrophies and their frequent association with mental defects.

In a review of the more accessible literature we have found 117 cases reported since Leblanc's thesis in 1897. This makes 195 cases reported to date; 44 of these cases are total hemihypertrophy.

The case report which follows shows hypertrophy of the entire shoulder girdle, arm, hand and fingers except the thumb which is normal in size as compared with the thumb on the opposite side. The hypertrophy in this case apparently involves all the tissues including the bones.

Case Report. C. S. W., white male, aged thirty-five years, was admitted for treatment of diabetes mellitus, June 24, 1924. The family history is entirely negative for cancer, tuberculosis, diabetes, arthritis, obesity, cardiac or renal diseases and insanity. One brother has six toes on his right foot; no other history of congenital defects could be elicited. His general health has been excellent. He had measles, mumps, whooping cough, chicken pox and scarlet fever in childhood.

The patient states that his left hand, arm and shoulder have always been very much larger than the right. He says that he was born that way and that his mother attributes the enlargement of his left arm to something she saw about one month before his birth. The nevus over his arm, hand and shoulder has also been present since birth and it has neither increased or decreased in size since he can remember.

The Adjutant General's Office report of the patient's health while in the army is about as follows: He enlisted in the Coast Artillery Corps at Columbus Barracks, Ohio, November 14, 1914. The left hand, arm and shoulder are enlarged out of all proportion to the rest of the body; he is left handed. There is an extensive nevus over arm, hand and shoulder. He has a slight genu valgum. January 3 to 8, 1916, he was in the hospital for fracture of left wrist, both bones; April 16 to 18, 1916, alcoholism, acute; August 20 to September 11, 1922, he received hospital treatment for chronic gastric ulcer.

Since the patient fractured his wrist in 1916, he has preferred to use his right hand.

The patient's birth and development were entirely normal except for the overdevelopment of the left hand, arm, and shoulder. He began study in a rural school at about eight years of age and continued (four months each year) until the age of sixteen. In spite of the fact that he went to school only four months each year, he finished nine grades. He never had any trouble with his teachers; he found his school work easy and was very fond of arithmetic, history and geography.

A general physical examination on September 19, 1925, showed: Temperature, 98.3°; pulse, 78; respiration, 18; height, 65 inches; no evidence of pain or discomfort. A well-nourished man of about thirty-five years. There is an overdevelopment of the left arm and shoulder which is enlarged out of all proportion to the rest of the body.

Over the back of the hand, extensor surfaces of the arm and forearm, over the shoulder and over the pectoral fold of the chest is an extensive nevus, port-wine in color, superficial, not evident to touch, sinuous in outline and blanches completely on pressure. There is no increase in the growth of hair, no deformity of the nails, axillary temperatures the same. There is no increase in

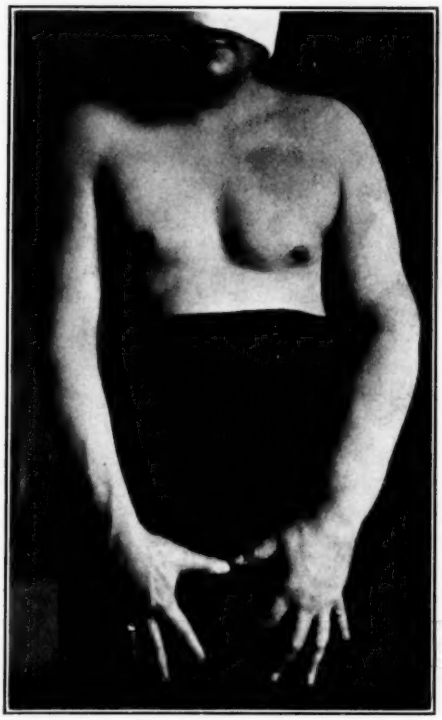

FIG. 1

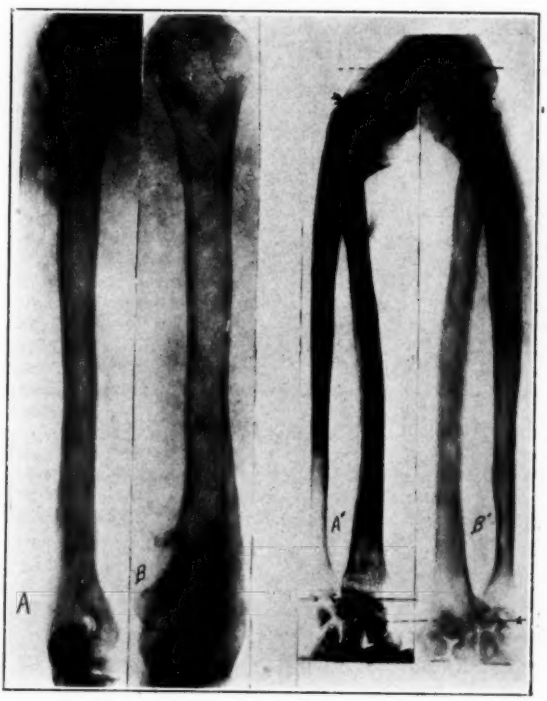

FIG. 2

sweating on the left side. The palm of the hand, flexor surface of the arm and axilla are not involved in the nevus. The veins of the left arm are more prominent than the right and are slightly varicose. The arm and shoulder are firm, with no edema and no increase in surface temperature. The rest of the skin is moist and clear. The hair distribution is of the normal male type. There is no enlargement of the lymph glands. The eyes show clear scleræ; extraocular movements are normally performed, the pupils are regular in outline and react to light and during accommodation. Ears, nose, mouth, teeth, tonsils and throat are in good condition. The thyroid is not enlarged. The thorax is asymmetrical; the left upper thorax is the larger; expansion is good and the bases descend well on inspiration. Percussion and auscultation elicited no abnormalities in the lungs. The heart is not enlarged the sounds are clear and there are no murmurs. The blood pressure was: systolic, 110; diastolic, 70; the same in both arms. In spite of the difference in the size of the arms, the radial pulse seem to be equal and synchronous, volume and tension the same on the two sides. The abdomen is soft, tympanitic, no masses, spasm or tenderness. The genitalia are normal, no scars or hernia. The deep tendon reflexes are equal and normal in the arms and legs. Rectal examination elicited nothing unusual. Ophthalmoscopic examination shows normal fundi.

MEASUREMENTS.

	Right side, cm.	Left side, cm.
Clavicle	19.0	20.0
Angle of Louis to 5th dorsal vertebra over arm over the deltoid muscle	50.5	52.5
Angle of Louis to 5th dorsal vertebra under arm	47.0	47.0
Circumference of arm at insertion of deltoid	31.0	45.0
Circumference of arm just above olecranon process	23.7	36.2
Circumference of arm 15 cm. below olecranon process	22.5	33.1
Circumference of arm at wrist	16.2	22.5
Length of second finger from metacarpophalangeal joint to end of finger	10.6	15.3
Circumference of thumb over middle of first phalanx	7.5	7.5
Circumference of index finger over middle of first phalanx	7.5	9.3
Circumference of second finger over middle of first phalanx	7.9	9.3
Circumference of ring finger over middle of first phalanx	6.2	8.7
Circumference of little finger over middle of first phalanx	6.0	7.5
Circumference at middle of palm of hand	21.2	28.7

Laboratory findings include the following: The urine contains no albumin or casts. Urine analyses vary from time to time, occasionally the urine is positive for sugar. The blood sugar varies from 150 to 200 mgm. per 100 cc. of blood. Noguchi com-

plement-fixation test for syphilis is negative, with both antigens, the Kolmer quantitive test, negative, the blood Wassermann, negative. The feces contain no ova or parasites. Blood examination shows: Red blood cells, 5,001,200; hemoglobin, 93 per cent (Dare); white blood cells, 9200; with a normal differential count.

BLOOD CHEMISTRY.

Non-protein nitrogen (mg. per 100 cc. blood)	30.00
Urea nitrogen (mg. per 100 cc. blood)	12.00
Uric acid nitrogen (mg. per 100 cc. blood)	3.80
Creatinine (mg. per 100 cc. blood)	1.50
Sugar (mg. per 100 cc. blood)	170.00
Chlorides (mg. per 100 cc. blood)	480.00
Cholesterol (mg. per 100 cc. blood)	209.00
Plasma CO_2 (volume per cent)	49.00

Fluoroscopic and Roentgen ray studies of the gastrointestinal tract revealed no defects. Roentgen ray and fluoroscopic examinations of the heart, lungs, mediastinum and great vessels elicited nothing abnormal. Roentgen ray pictures of the skull and sella turcica are perfectly normal. Roentgen ray of the left arm shows uniform hypertrophy of the bones, an old fracture of the left wrist and a peculiar spur on the lower inner border of the radius. The Roentgen ray plates of the two arms were made under identical conditions. Following are comparative measurements:

	Right side.	Left side.
Clavicle	19.3 cm.	20 cm.
Humerus	37.5 cm.	38 cm.
Radius	25.5 cm.	29 cm.
Ulna	28.0 cm.	30 cm.

The bones of the left arm are from $\frac{1}{4}$ to 1 cm. greater in diameter than the corresponding bone of the right side.

A section of the skin and subcutaneous tissue was removed from the extensor surface of the left arm under local anesthesia for microscopic study. The section showed normal skin and increased subcutaneous fat.

Special Features. In 68 per cent of the cases the right side of the body is involved; in about 30 per cent of the cases there is some sort of skin involvment: Nevus, venous hyperemia, telangiectasis, elephantiasis, pigment anomalies, abnormal growth of hair, varicosities, nevus pilosis, angioma, and kerotosis have been mentioned.

As in any anomaly arising during embryonic life, there are many peculiar features which are best illustrated by giving the combination of these as they occurred along with the hypertrophies: Increase in temperature on the affected side, Redard;[23] increased salivation and taste more acute on side of the affection, Friedreich;[12] thymus enlargment and one kidney hypertrophied, Hutchinson's[16] case which came to autopsy; tongue and teeth hypertrophied, Passauer;[22]

right side of brain enlarged, Steffen;[24] thyroid absent, Thompson;[26] hypertrophy of fingers and toes on opposite sides of the body has been noted several times, Brünning's[4] case; right optic thalamus enlarged, McGregor;[18] increased sugar tolerance, Cohen;[6] increased temperature and sweating, synostosis of proximal phalanges, Maschke;[19] tenderness over the hypertrophied part, and for this reason considered a morbid entity, Möbius;[20] hyperplasia of the bone, fatty and connective tissues, thickening of the nerve sheaths, enlargement and thickening of the arteries and increase in the size of the muscle fibers, Hornstein's[14] autopsy report. Krivall operated on a case and found principally fatty tissue involved. Redard found fatty tissue involved and considered his case of a lymphatic origin. Campbell's[5] case of congenital hemihypertrophy with involvement of the nerve trunks was interesting in that it included two congenital anomalies, namely, hemihypertrophy and neurofibromatosis. Gessell reviewed the literature very carefully and found subnormal mentality in 13 per cent of the case reports; he believes that if careful study had been made, perhaps the incidents of subnormal mentality would have been higher.

Telford[25] calls attention to the frequent association of localized hypertrophy, nevus formation and varicose veins. He, and many other writers believe this triad to form a definite clinical entity. The disease when fully developed presents three features, of which the nevus and hypertrophy are congenital, but become more apparent as the patient grows older. The varices appear sometime later on, or may be altogether lacking. The French have been most active in writing on this symptom triad.

It is interesting to note that the family histories are for the most part entirely negative of congenital deformities. However, Leblanc reports one family in which several members showed congenital hypertrophy of the left hand. It is noted that in our case report one brother had polydactylism. This has been noted by several observers before our case report.

Etiology and Comments. From time to time many speculations have been made as to the etiology of the anomaly. The number of theories advanced makes it evident that, in the light of our present knowledge, we are unable to do more than to speculate. Most writers agree that the anomaly is embryologic, however, the wide variation of opinions can only be shown by enumeration of a few: Vasomotor paralysis; arrested development of different coats of the arteries; intrauterine meningitis; faulty development of the spinal cord and enlargement of one side of the cerebrum, central nervous system lesions; disturbances of the glands of internal secretion—possibly hyperpituitarism; deviation in the normal process of twinning; the peculiar biological theory of Fortescue-Brickdale;[11] increased blood supply to the parts; interference with the lymph return and vasomotor paralysis. Many writers have expressed an

opinion that the condition is due to hyperpituitarism, but there is no proof of this. Most recent writers seem to think that the theory, above mentioned, of a deviation in the normal process of twinning, advanced by Gessell is the most plausible one at the present time. Is not the plausibility of this theory merely due to our gross ignorance of what really constitutes "normal twinning?"

The speculations above noted pretty well cover the domain of pathology and its application to embryologic and biologic sciences in their applications to growth and development. In reviewing the literature one is impressed by the almost universal rule: for each case there is a theory. From what has been learned and written, we are left with the impression that there is somehow produced an irrevocable change in the tissues of the affected part, or parts, during embryonic life for which we cannot assign a reason.

Summary. 1. The more accessible literature has been reviewed.

2. The history and the various congenital defects that occur along with the hypertrophy have been mentioned and the various theories of etiology enumerated.

3. There is substantial agreement that the cause of the anomaly is some prenatal disturbance, although the exact nature of the lesion or the period in embryologic development in which it occurs is absolutely unknown.

4. In only a few case reports is there any indication that the patient suffered inconvenience from the anomaly.

I wish to express my indebtedness to Dr. R. W. Hutchinson, head of the Roentgen ray department of the Naval Hospital; to the photographic department of the Naval Medical School and especially to E. M. Bullock, chief pharmacist's mate, who made the pictures and reduced the Roentgen ray plates.

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BLOOD-SERUM CALCIUM IN SPRUE AND OTHER PATHOLOGIC STATES IN THE TROPICS.*

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In March, 1925, the writers, one representing the medical and the other the chemical phase of the problem, united in an effort to determine the extent and significance of calcium deficiency in the blood serum in inhabitants of Porto Rico, particularly with regard to sprue and its common background, the syndrome of nutritional unbalance so frequently observed in this island.

The symptom-complex of this condition, resulting in what has been referred to, rightly or wrongly, as "glandular insufficiency," has been already presented and discussed by one of us in a previous paper.[1] In this exhaustion process the digestive glandular functions have been involved most patently, and those of the endocrines, due to the well-known lack of sufficient methods of precision today at our command, more vaguely. Briefly, this syndrome consists of an acid fermentative disorder of the digestive tract, with constipation, or constipation interrupted at times by brief spells of soft,

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fermented stools; asthenia and loss of weight; vague nervous symptoms, such as psychic irritability, or mental hebetude; cramps in the limbs and mild myalgic pains in the body; eventually, diminution in the size of the liver and the development of symmetrical areas of pigmentation of the skin, most noticeable over the forehead and malar prominences.

This collection of symptoms is banal the world over and is in no sense tropical, save in its frequency and intensity in the hot countries. We do not presume to discuss its varied etiology in other climes, but in this island it seems to possess at least one parent in an irrational dietary. Whatever we may choose to call it, it is out of just such cases, and, as a rule, quite definitely, that sprue is born, and sprue is, to say the least, not a prevailing disease of temperate and northern climates where the opportunities for nutritional unbalance are at times fully as rich in possibilities. To invoke mysterious rays, supposed to be more frequent and intense in the torrid zone, is more or less pure speculation, and to refer to the degradation of the species in the tropics is only another way of expressing the heredity transmission of a poorly nourished cell.

In 1921 or 1922 one of the writers became impressed with the reported calcium-balancing function of the parathyroids upon the blood, and having been influenced by the apparent benefit to some of his patients from the oral administration of calcium lactate, he combined this latter with small doses of parathyroid gland extract. A year's experience soon demonstrated that parathyroid by the mouth was of no benefit, and it was abandoned. The reported benefit from this combination on the part of others gave rise to the present research.

The first step was to establish the calcium content in the blood serum of normal persons in Porto Rico. For this purpose, through the coöperation of their Colonel, volunteer donors of samples of blood were solicited from soldiers of the 65th Infantry, U. S. Army, all native born and most of them representatives of the best physical types in the island. These men had been brought to a high state of physical fitness by exercise, regular habits and the Army ration, and were, in fact, the only class available to demonstrate the Porto Rican at his physical best. The men had been already shown the value of proper food by the investigation and elimination of beriberi,[2] which appeared among them some three or four years ago, and we were able to secure without demur on their part 96 men considered healthy and fit by their medical officer, Capt. J. H. Blackwell.

The results of the estimation of their serum calcium appears in Table I. In temperate climates, considering from 9 to 12 mg. per 100 cc. as the normal limits of total serum calcium (9.2 to 11.3, Howland and Marriott, cited by Collip), and from 4.5 to 6 mg. for the diffusible calcium, then 17.7 per cent of these healthy soldiers

fell below normal in their total, and 38.52 per cent in their diffusible serum calcium, with an average for the individual of 9.6 and 4.69 mg., respectively. It is interesting to compare this result with that of Schwartz and Levin,[3] who determined the total calcium of the serum of 310 persons, all suffering from some variety of skin disease in a northern clinic, which averaged 9.85 mg. It seems proper, therefore, to consider the serum calcium in healthy persons of this tropical island somewhat low.

TABLE I.—TOTAL AND DIFFUSIBLE SERUM CALCIUM IN HEALTHY AND DISEASED PORTO RICANS.

Total serum calcium, mg. per 100 cc.	Healthy soldiers.		Syndrome nutritional unbalance of Porto Rico.	
	No.	Per cent.	No.	Per cent.
Over 12	1	1.04		
Over 11	6	6.25	3	2.97
10.5–11.0	5	5.20	7	6.93
10.0–10.5	7	7.29	11	10.89
9.5–10.0	31	32.29	18	17.82
9.0– 9.5	29	30.20	16	15.84
Low Normal Limit.				
8.5– 9.0	12	12.50	25	24.75
8.0– 8.5	5	5.20	12	11.98
7.5– 8.0	..	...	4	3.96
7.0– 7.5	..	...	5	4.95
Total	96	99.97	101	99.99
Diffusible serum calcium.				
Over 6.5	2	2.08		
6.0–6.5	3	3.12	2	1.98
5.5–6.0	10	10.41	6	5.94
5.0–5.5	11	11.45	11	10.89
4.5–5.0	33	34.37	15	14.85
Low Normal Limit.				
4.0–4.5	23	23.95	22	21.78
3.5–4.0	9	9.37	24	23.76
3.0–3.5	5	5.20	17	16.83
2.5–3.0	..	...	4	3.96
Total	96	99.95	101	99.99

Average total calcium: Healthy series, 9.60 mg.; nutritional series, 9.20 mg.
Average diffusible calcium: Healthy series, 4.69 mg.; nutritional series, 4.20 mg.

By contrast with these, a study of the serum calcium of 101 persons suffering from the syndrome of nutritional unbalance above described for this island was made. In this group 45.64 per cent fell below the minimum for total and 66.33 per cent for diffusible serum calcium. Such figures are really abnormal. In sprue, of which there are 55 cases reported in Table II, 47.25 per cent and 72.71 per cent are below the minimum for total and diffusible calcium, respectively. In the 47 cases of sundry diseases without any clinical evidence of sprue (Table V) these percentages are respectively 44.66 and 62.74.

TABLE II.—TOTAL AND DIFFUSIBLE SERUM CALCIUM IN SPRUE.

Total serum calcium, mg. per 100 cc.	Grade of disease.				Total.	Per cent.
	Mild.	Moderate.	Severe.	Cachexia.		
Over 10.5	..	1	2	1	4	7.27
10.0–10.5	1	..	1	1	3	5.45
9.5–10.0	..	..	9	4	13	23.63
9.0– 9.5	1	1	3	4	9	16.36
8.5– 9.0	2	1	2	4	9	16.36
8.0– 8.5	3	2	3	1	9	16.36
7.5– 8.0	..	1	1	3	5	9.09
7.0– 7.5	..	..	1	1	2	3.63
5.90	1	..	..	..	1	1.81
Total	8	6	22	19	55	99.96
Diffusible serum calcium.						
6.90	..	..	1	..	1	1.81
5.5–6.0	..	..	1	2	3	5.45
5.0–5.5	..	1	3	1	5	9.09
4.5–5.0	1	2	3	..	6	10.90
4.0–4.5	4	1	7	3	15	27.27
3.5–4.0	1	..	4	4	9	16.36
3.0–3.5	1	..	4	5	10	18.18
2.5–3.0	..	1	..	1	2	3.63
2.0–2.5	1	..	1	2	4	7.27
Total	8	5	24	18	55	99.96

Average total calcium, 9.02 mg. per 100 cc. blood.
Average diffusible calcium, 4.11 mg. per 100 cc. blood.

So far, therefore, sprue shows the lowest serum calcium values, although there is not sufficient difference between the three pathologic classes to warrant the statement that sprue can be distinguished from the others by any such insignificant calcium deficiency. Least of all can this statement be justified when we view the extreme individual irregularity of the components of this table. Over one-half of the severe and cachectic cases, in which the disease was so apparent that any other diagnosis would have seemed impossible, gave normal total calcium values (Scott's "ionic" calcium?), while one-fourth gave a normal diffusible calcium.

All doubt on the unreliability of total or diffusible calcium values, either for diagnosis or prognosis in sprue, is removed by Table VI. In this table, comprising serum calcium estimations of 456 of the inmates of our insane asylum, 57.48 per cent were below the normal minimum in total and 79.36 per cent in diffusible calcium, with an average for the individual of 8.7 and 3.69 mg. per cent, respectively. Thus, low total serum calcium values as pathognomonic of sprue, or of any other special disease we have so far seen, are not substantiated by these figures.

To what, then, can they be attributed? That they are the indirect results of nutritional unbalance seems more than likely. The marasmus of sprue is notorious. No disease furnishes a higher percentage of "living skeletons," but there is still to be explained

the fact that in more than one-half of the severe and cachectic cases we have a normal total serum calcium.

TABLE III.—CASES OF SPRUE WHICH RECEIVED NO PARATHYROID NOR CALCIUM IN ANY FORM BEFORE ESTIMATING THE SERUM CALCIUM.

Name.	Total calcium.	Diffusible calcium.	Hemoglobin, per cent.	Loss of weight from sprue, pounds.	Form of disease.
J. F.	9.1	5.9	40.0	46.0	Cachexia.
J. B.	9.9	5.2	45.0	19.0	Cachexia.
F. E.	10.5	4.3	34.0	19.0	Cachexia.
C. R.[1]	10.8	6.8	70.0	25.0	Severe.
R. B.[2]	10.1	2.3	92.0	17.0	Mild.
A. G.	8.1	4.3	30.0	58.0	Severe.
G.	9.5	2.0	85.0	28.0	Severe.
J. B.	8.4	5.0	60.0	..	Severe.
B. C.	8.1	4.4	80.0	16.0	Mild.
P. G.	7.5	3.3	50.0	..	Cachexia.
R. Q.	8.5	4.6	88.0	..	Mild.
C. T.	9.0	3.1	45.0	50.0	Cachexia.
B. R.	8.4	3.4	42.0	6.0	Severe.
W.	10.1	3.6	..	..	Acute; severe.
P. M.	9.9	5.2	85.0	56.0	Severe.
A. G.	9.2	4.3	..	..	Mild.
B. G.	9.0	4.9	..	7	Severe.
J. M. S.	7.2	3.8	65.0	8.0	Severe.
C. G.	8.5	3.2	50.0	17.0	Severe.
V. R.	9.9	4.3	..	32.0	Severe.
R.	8.8	4.3	..	..	Moderate.
T. N.	10.3	4.4	..	..	Cachexia.
V. V.	8.6	3.8	..	..	Severe.
I. V.	8.0	4.3	..	3.0	Mild.
L. C.	8.1	4.1	..	40.0	Severe.
A. P.	8.3	4.3	50.0	46.0	Cachexia.
P. G.	7.6	3.4	40.0	26.0	Cachexia.
F. J.	8.8	4.1	85.0	16.0	Severe.
Average	8.9	4.0	63.1	26.6	Mild, 17.8 per cent. Moderate, 3.5 per cent. Severe, 50 per cent. Cachexia, 28.5 per cent.

In 27 cases which received parathyroid and calcium intermittently by mouth before calcium estimation the average total serum calcium was 9.07 mg. per cent; of their diffusible calcium, 3.92.

[1] A year ago vaccine only; no medicine; no diet; gain of weight.
[2] Severe case a year ago; vaccine and gain of 49 pounds in weight.

To clear up this, and the still more important question of the efficacy of parathyroid gland extract in the treatment of sprue, we secured two batches of injectable parathyroid from a commercial source whose reliability is unquestioned. To one set of 24 cases we administered one of these lots, and to the other of 26 cases the other. The results are seen in Tables IX and X. From these tables we can gather that there seems to be, as a rule, a real and positive rise in serum calcium after the intramuscular injection of parathyroid extract. This rise must be only temporary, however,

as may be faintly shadowed by the disparity between rises after a month and those after a day or so following injection. On the other hand, some of our old cases of sprue, not in these tables, have attained a normal calcium with diet alone, even with Monilia vaccines alone, but always only in conjunction with improved nutrition, by improved digestion, by restoration of digestive glandular efficiency. In spite of all this, we are inclined to agree with Collip, that he has found a specific parathyroid hormone, that he has standardized it, and that he has given us a valuable means of temporarily restoring serum calcium until by improved nutrition the patient can be definitely cured.

TABLE IV.—COMPARISON BETWEEN SYNDROME OF NUTRITIONAL UNBALANCE IN PORTO RICO AND SPRUE.

	Sprue.		Nutritional unbalance syndrome.	
	No.	Per cent.	No.	Per cent.
Raw tongue and white, frothy diarrhea	23	41.8		
One or the other of above	19	34.5		
Acid fermentative diarrhea only	11	20.0	6	5.9
Excoriation of tip and edges of tongue	..	..	12	11.8
Subjective stinging of tongue	..	..	11	10.8
Occasional loose bowels	..	..	11	10.8
Diarrhea alternating with constipation	..	..	28	27.7
Constipation only	..	..	31	30.6
Neither diarrhea nor constipation	..	..	31	30.6
Excessive intestinal gas	52	94.5	75	72.4
Excoriation of anus	41	74.5	36	35.6
Irritability of nervous system	49	89.0	84	83.1
Asthenia	52	94.5	78	77.2
Numbness of extremities	42	76.3	49	48.5
Muscular cramps of extremities	31	56.3	43	42.5
Myalgia	40	72.7	76	75.2
Symmetrical pigmentation of face and body	38	69.0	41	40.5
Number of cases of sprue				55
Mild form			8	
Moderate form			6	
Severe form			22	
Cachexia			19	
Number of cases of syndrome nutritional unbalance				101

Average loss of weight of sprue cases,[1] 23.5 pounds (44 cases); nutritional syndrome (65 cases), 12.5 pounds.

[1] In 44 of the total 55 cases the loss was 25.3 pounds per case; of the 23 cases with a complete classical picture of sprue, 20 were found to have lost an average of 29 pounds. The average hemoglobin percentage of 31 of the 55 sprue cases was found to be 60.

How much or how little this has to do with the cure of a case of sprue we do not know, but we have not as yet seen anything to make us believe that it is an all-important remedial agent. On the contrary, we have had some very obstinate and extreme cases of sprue which have not appeared to have been bettered by this treatment, long and persistently applied. It is probably one of the many

things which we can do to improve the condition of the patient, but it is by no means to be compared with the efficacy of diet.

TABLE V.—TOTAL AND DIFFUSIBLE CALCIUM IN SUNDRY DISEASES OTHER THAN SPRUE.

Calcium per 100 cc. of blood, mg.	Nervous diseases.	Vascular diseases.	Respiratory diseases.	Intestinal diseases.	Surgical diseases.	Skin diseases.	Syphilis.	Tuberculosis.	Beriberi.	Pernicious anemia.	Exophthalmic goiter.	Total.	Percentage.
Total calcium.													
10.5–11.0	2	1	..	..	..	1	..	..	..	..	1	5	10.6
10.0–10.5	1	..	1	..	..	1	..	..	..	..	..	3	6.3
9.5–10.0	1	1	..	1	..	..	..	..	..	1	..	4	8.5
9.0– 9.5	4	1	1	1	1	1	2	3	..	..	..	14	29.7
8.5– 9.0	2	1	2	..	2	..	..	..	..	..	..	7	14.8
8.0– 8.5	1	2	..	..	1	1	..	4	1	..	..	10	21.2
7.5– 8.0	1	..	..	..	..	..	..	1	..	..	..	2	4.2
7.0– 7.5	..	..	..	..	..	..	1	1	..	..	..	2	4.2
Total	12	6	4	2	4	4	3	9	1	1	1	47	
Average mg.	9.35	9.03	9.17	9.58	8.33	9.38	8.74	8.39	8.04	9.55	10.9	9.04	
Diffusible calcium.													
6.5–7.0	..	..	..	..	..	..	..	..	1	..	1	2	4.2
6.0–6.5	1	1	..	..	..	..	..	1	..	..	..	3	6.3
5.5–6.0	..	2	1	..	1	..	..	1	..	..	..	5	10.6
5.0–5.5	3	..	..	..	..	..	..	..	..	..	..	3	6.3
4.5–5.0	..	1	..	1	..	..	1	..	..	1	..	4	8.5
4.0–4.5	3	2	..	..	..	1	1	..	..	..	..	7	14.8
3.5–4.0	2	..	2	1	3	..	..	1	..	..	..	9	19.1
3.0–3.5	3	..	..	..	..	2	1	4	..	..	..	10	21.2
2.5–3.0	..	..	1	..	..	1	..	1	..	..	..	3	6.3
2.0–2.5	..	..	..	..	..	..	..	1	..	..	..	1	1.0
Average mg.	4.23	5.22	3.84	4.30	4.15	3.51	3.97	3.62	6.77	4.60	6.57	4.23	

Average total calcium, 9.04 mg. per 100 cc.
Average diffusible calcium, 4.23 mg. per 100 cc.

An important result of these injections of Collip's extract was a confirmation of a statement frequently made by one of us to the effect that cramps in the extremities, particularly in the legs, so frequently complained of by our patients with the syndrome of nutritional unbalance here in Porto Rico, and by others with sprue, was, in effect, tetany. In almost every case muscular cramps in these pathologic states have abruptly disappeared after an injection of parathyroid extract. We have never observed hypercalcemia, in spite of "pyramiding" of doses, as will be seen in Table IX, where three injections of 2 cc. have been given daily on several occasions. In only 1 case has any untoward symptom occurred, and this was after the seventh of a series of 1 cc. injections in batch 2, Table X, in which a severe headache supervened immediately after the injection, lasting twenty-four hours. No other symptom made itself manifest, and the patient is now well.

TABLE VI.—TOTAL AND DIFFUSIBLE CALCIUM IN INMATES OF THE INSANE ASYLUM OF PORTO RICO.

Calcium per 100 cc. of blood, mg.	Involutional insanity.	Mental depressive insanity.	Dementia precox.	Psychosis, manic depressive.	Psychosis, senile.	Inferior degeneracy and imbecility.	Alcoholic insanity.	Epilepsy with psychosis.	Cerebral syphilis with psychosis.	Periodic insanity.	Puerperal insanity.	Paranoia and secondary dementia.	Miscellaneous.	Total.	Percentage.
Total calcium.															
Over 11	2	1	1	2	...	1	...	...	1	...	...	...	...	8	1.7
10.5–11.0	2	3	4	6	...	...	...	1	1	3	...	2	1	23	5.0
10.0–10.5	1	5	4	3	1	1	1	...	3	2	2	6	3	32	7.0
9.5–10.0	7	13	7	3	2	3	1	4	1	4	3	3	...	51	11.3
9.0– 9.5	4	15	15	10	4	1	1	2	5	5	2	4	4	72	15.7
8.5– 9.0	6	12	20	8	4	4	4	1	6	2	3	10	2	82	16.7
8.0– 8.5	7	20	27	12	...	4	4	6	1	2	...	12	3	98	21.4
7.5– 8.0	2	6	4	12	2	...	4	4	3	1	...	8	...	46	10.0
7.0– 7.5	1	3	8	7	...	2	1	2	2	3	1	3	3	36	7.8
6.5– 7.0	...	1	...	3	...	...	1	...	...	...	...	1	...	6	1.3
6.0– 6.5	...	...	...	...	...	...	...	...	...	...	...	1	...	1	0.2
5.5– 6.0	...	...	...	...	...	...	...	...	1	...	...	...	...	1	0.2
Total	32	79	90	66	13	16	17	20	24	22	11	50	16	456	
Average mg.	9.17	8.90	9.41	8.67	8.98	8.83	8.32	8.61	8.77	9.12	8.52	8.58	8.83	8.70	
Diffusible calcium.															
Over 6.5	...	1	1	...	1	...	...	...	...	...	...	...	...	3	0.6
6.0–6.5	2	1	...	...	...	...	...	...	...	...	...	...	1	4	0.8
5.5–6.0	1	4	3	1	1	...	...	2	...	4	...	3	...	19	4.1
5.0–5.6	1	2	8	...	...	...	...	...	3	2	1	2	...	19	4.1
4.5–5.0	5	14	12	3	3	...	3	1	1	...	1	3	3	49	10.7
4.0–4.5	8	15	10	16	2	1	1	6	3	5	3	7	2	79	17.3
3.5–4.0	9	15	18	1	1	4	3	5	6	3	3	11	4	100	21.9
3.0–3.5	2	16	19	21	3	8	4	5	5	7	2	15	3	110	24.1
2.5–3.0	2	7	14	4	1	3	5	1	2	...	1	6	1	47	10.3
2.0–2.5	1	3	5	2	1	...	...	...	4	1	...	3	2	22	4.8
1.5–2.0	1	1	...	1	...	...	1	...	...	...	...	...	...	4	0.8
Average mg.	4.06	3.94	3.81	3.61	4.19	3.32	3.48	3.90	3.59	4.08	3.81	3.66	3.75	3.69	

Average total serum calcium, 8.7 mg. per cent.
Average diffusible calcium, 3.69 mg. per cent

A few words should be added concerning the supposed beneficial effect from the oral administration of parathyroid extract and calcium. First, as to calcium, given by one of us in the form of lactate in doses of 0.65 gm., three times daily on an empty stomach: Among the facts so far accumulated concerning sprue there are four which may relate to this question: (1) The feces are apt to be highly acid; (2) the percentage of undigested fat, and very especially of fatty acids, is extraordinarily high, that is, there is a great reduction in fat absorption; (3) the duodenal lipase is apt to be abnormally low, often intermittently absent; (4) the serum calcium is frequently low. Now, as will be seen later, and from an overwhelming amount of scientific evidence from other sources, the administration of calcium lactate cannot be depended upon to raise the serum calcium when given orally. But the use of calcium in sprue is nevertheless sanctioned by favorable results attested by a large number of physicians who have had to treat it. We have not infrequently seen improvement, usually gradual and only at times noticed by the patient, from the long and regular administration of calcium in this disease.

As to parathyroid extract given orally: Granting this slight improvement in the general condition from the use of calcium, no further advantage was gained by its combination with parathyroid in 0.1 gr. doses, obtained from a reliable biologic products company. Forty-five persons suffering from either pure nutritional unbalance, as above described, or from unequivocal sprue, had been taking these two drugs in doses specified three times a day for varying periods throughout about a year. Their calcium was not estimated before they began, as at that time we were engaged in other problems, but the fact remains that after an average of 255 such doses they were found to have at the end of that time an average total serum calcium of 9.09 mg. per cent, and a diffusible calcium of 4.09 mg., not essentially different from the average of untreated cases of sprue and nutritional unbalance rehearsed in this paper. Of these 45, 22 were of sprue, many of them severe or cachectic cases. Eighteen of the 22 had been taking parathyroid and calcium up to the very day on which their calcium estimation was made and, nevertheless, the average of their total serum calcium was 8.92, of their diffusible 3.9 mg. per cent., figures indistinguishable from those of sprue which were examined before any treatment. In fact, these 22 persons had received an average of 286 doses of these drugs before their examination.

In Table II an estimate of the serum calcium was made in all cases of sprue accounted for in this paper. Of these 55 cases, however, 27 had received parathyroid and calcium at some time previous to their examination. While we discount the supposed effect of such medication in raising the serum calcium, out of

Average total serum calcium, 8.7 mg. per cent.
Average diffusible calcium, 3.69 mg. per cent

respect to those in whose minds a doubt might arise as to a possible influence therefrom, we have separated the two groups in Table III The first group received no parathyroid nor calcium previous to their examination; the second group had received them. The difference between these groups also fails to lead support to those who believe the oral administration of parathyroid and calcium efficacious.

TABLE VII.—COMPARISON BETWEEN CALCIUM OF SERUM AND CEREBROSPINAL FLUID IN 34 INSANE PATIENTS.

Diagnosis.	No. of days between examinations.	Blood-serum calcium.		Cerebrospinal-fluid calcium.		Difference between serum and cerebrospinal fluid calcium.	
		Total.	Diffusible.	Total.	Diffusible.	Total.	Diffusible.
Psychosis, epileptic	0	7.4	3.3	4.8	3.9	−2.6	+0.5
Psychosis, manic depressive	0	8.9	3.1	4.0	2.9	−4.9	−0.1
Dementia, secondary	3	7.0	3.9	5.5	4.8	−1.5	+0.8
Cerebral syphilis with epilepsy psychosis	14	9.9	5.2	4.3	3.5	−5.5	−1.6
Psychosis, manic depressive	4	6.8	3.7	5.4	3.5	−1.4	−0.2
Psychosis, epileptic	25	9.6	3.5	5.6	2.9	−4.0	−0.5
Paranoia	16	9.8	3.4	5.2	2.7	−4.6	−0.6
Psychosis, cerebral syphilis	7	9.2	4.2	5.4	2.5	−3.7	−1.7
Manic depressive insanity	0	9.5	4.1	4.7	2.2	−4.8	−1.9
Dementia precox	7	8.0	2.5	4.4	4.0	−3.8	+1.5
Paranoia	...	..	..	4.9	3.6		
Dementia precox	7	8.8	4.0	4.2	2.8	−4.6	−1.1
Dementia precox	15	7.1	3.4	4.7	2.9	−2.4	−0.4
Psychosis, cerebral syphilis	13	9.0	3.9	4.2	2.9	−4.8	−0.9
Dementia precox	10	8.5	3.2	4.5	2.8	−4.0	−0.4
Inferior degeneracy	13	8.6	3.1	4.3	2.5	−4.2	−0.5
Psychosis, manic depressive	7	8.2	3.9	4.6	3.9	−3.6	+0.04
" " "	15	9.0	4.2	6.0	3.6	−3.0	−0.5
" " "	0	7.6	3.5	4.4	3.7	−3.2	+0.2
Psychosis, cerebral syphilis	18	7.2	3.6	4.3	3.3	−2.8	−0.2
Psychosis, epileptic	76	9.3	4.4	3.9	3.6	−5.4	−0.8
Inferior degeneracy	76	7.2	3.6	4.4	3.5	−3.2	−0.1
Psychosis, epileptic	76	9.7	2.9	4.5	3.4	−5.1	+0.5
Dementia precox	3	9.0	4.2	4.5	1.8	−4.5	−2.4
Undetermined	...	..	..	4.8	3.5		
"	...	..	..	5.1	3.1		
Idiocy	13	7.4	3.0	4.7	2.0	−2.7	−1.0
Dementia precox	21	10.8	3.1	5.4	2.8	−5.4	−0.3
Psychosis, epileptic	23	8.2	3.5	5.4	3.2	−2.7	−0.3
Psychosis, cerebral syphilis	0	7.8	3.7	4.4	2.8	−3.3	−0.8
Dementia precox	5	8.4	3.2	4.7	3.2	−3.6	−0.07
Manic depressive insanity	13	7.7	3.1	4.7	2.7	−3.0	−0.4
Psychosis, epileptic	23	7.9	4.1	4.6	2.7	−3.2	−1.4
Manic depressive insanity	13	8.5	4.5	5.2	3.5	−3.3	−0.9
Average	...	8.4	3.6	4.7	3.1	−3.7	−0.6

TABLE VIII.—PERCENTAGE OF DIFFUSIBLE TO TOTAL CALCIUM.

Percentage diffusible to total calcium.	Healthy.		Nutritional unbalance.		Sprue.		Sundry diseases.		Insane.		Tota No.
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
Over 80	..	..	..	..	..	..	1	2.1	1	0.1	2
Over 70	..	..	2	2.0	..	..	..	..	5	1.1	7
Over 60	6	6.3	6	5.9	4	7.3	7	14.9	23	5.0	46
55 to 60	14	14.6	8	7.9	3	5.5	5	10.6	27	5.9	57
50 to 55	21	21.9	12	11.9	13	23.6	4	8.5	68	10.5	118
45 to 50	28	29.9	20	19.8	7	12.7	7	14.9	62	13.6	124
40 to 45	19	19.8	30	29.7	14	25.5	9	19.1	106	23.2	178
35 to 40	6	6.3	13	12.9	7	12.7	7	14.9	80	17.5	113
30 to 35	2	2.0	8	7.9	3	5.5	6	12.7	49	10.7	68
25 to 30	..	..	2	2.0	1	1.8	..	..	23	5.0	26
20 to 25	..	..	..	..	3	5.5	1	2.1	9	1.9	13
15 to 20	..	..	..	..	..	..	..	..	3	0.6	3
Total	96	..	101	..	55	..	47	..	456	..	755
Average	48.9	..	45.5	..	44.7	..	45.2	..	43.8		

Method of Estimating Calcium in Blood Serum. The serum calcium was estimated by Tisdall's modification of Kramer and Tisdall's method.[4] In order to check upon ourselves and this method itself, we at first ran a series in which both the Tisdall's modification and the gravimetric method were employed in the same cases. Our results were so close that they lay within 0.02 mg. of each other, but as the gravimetric method required too much blood it was abandoned in favor of the Tisdall-Kramer and Tisdall technique. This method of calcium determination, which is the only one used in making up our tables, was performed as follows: To 2 cc. of clear serum in 15 cc. centrifuge tubes are added 2 cc. of boiled water and 1 cc. of a 4 per cent ammonium oxalate solution. This mixture is allowed to stand thirty minutes to an hour. The tubes are now centrifuged at a velocity of 2000 revolutions per minute for ten minutes when the precipitate will be found to be well packed at the bottom of the tube. The supernatant liquid is carefully poured off, and, holding the tube inverted, its mouth is wiped dry with a bit of gauze, and it is placed, inverted, upon a filter paper for five minutes to drain and dry. This precipitate and the sides of the tube are now washed by a fine stream, directed from a wash bottle, of 3 cc. dilute ammonia water (2 cc. of concentrated ammonia in 98 cc. of distilled water). The resulting suspension is again centrifuged and drained as described, and 2 cc. of normal sulphuric acid are added to the precipitate. This acid is blown from a pipette directly upon this precipitate so as to break up the mat and facilitate solution.

The tube and its contents are now placed in a water-bath at boiling temperature, and the oxalic acid is titrated with a 0.01/N potassium permanganate solution, using a microburette.[5] This permanganate solution is freshly standardized for each estimation. The only difference between our practice and that given by Tisdall's method is that we employ but one washing of the precipitate with 3 cc. of ammonia water instead of two washings of 4 cc. each.

The check which we placed upon our titration method was Alport's gravimetric method of estimating blood calcium, as modified by Cameron and Moorhouse:[6]

TABLE IX.—RESULT ON SERUM CALCIUM OF INJECTABLE PARATHYROID (GROUP 1).

Case.	Total calcium.	Diffusible calcium.	Number of days before injection.	Number of times injection was given × dose on each occasion.	Period of days consumed in injecting the entire amount.	Total calcium.	Diffusible calcium.	Days elapsed after injection before the calcium was reestimated.	Total calcium.		Diffusible calcium.	
									Gain.	Loss.	Gain.	Loss.
1 ..	6.7	..	5	9 × 0.5	13	8.8	..	1	2.0			
	8.8	..	1	5 × 2.0	7	8.9	..	1	0.1			
2 ..	10.8	..	0	2 × 1.5	1	9.9	..	1	..	0.8		
	9.9	..	0	5 × 2.0	5	9.4	..	2	..	0.5		
	9.4	..	1	3 × 2.0	3	9.4	..	2				
	9.4	..	1	2 × 2.0	2	9.1	2.2	49	..	0.3		
3 ..	9.3	..	9	3 × 1.5	5	9.7	..	0	0.4			
	9.7	..	3	2 × 2.0	4	9.2	..	3	..	0.5		
						9.8[1]						
						9.4	3.1[2]	..	0.6	0.4		
	9.4	3.1	1	3 × 2.0	1	9.4	3.0	1				
4 ..	8.1	..	12	2 × 2.0	1	9.4	..	1	1.3			
5 ..	8.8	..	31	5 × 2.0	3	9.1	..	..	0.2			
6 ..	10.2	4.5	13	6 × 2.0	3	8.5	2.5	1	..	1.7	..	1.9
						9.1	4.8[3]					
						9.1	4.6[3]					
						9.5	4.7[3]					
						9.5	4.7[3]					
7 ..	10.1	2.3	12	6 × 2.0	3	9.3	4.4	1	..	0.8	2.1	
8 ..	8.6	3.3	0	6 × 2.0	3	8.7	3.6	1	..	..	0.3	
9 ..	8.0	3.3	1	4 × 2.0	2	9.3	4.4	1	1.2	..	1.0	
10 ..	7.9	3.0	13	4 × 2.0	2	9.5	6.1	1	1.5	..	3.0	
11 ..	8.6	2.3	13	6 × 2.0	3	9.3	3.9	1	0.6	..	1.6	
12 ..	9.1	4.0	4	6 × 2.0	3	9.6	4.1	1	0.4	..	0.1	
13 ..	9.3	4.7	81	7 × 2.0	7	12.4	5.6	1	3.1	..	0.9	
14 ..	10.3	4.4	0	5 × 2.0	5	10.8	4.8	5	0.5	..	0.4	
15 ..	8.4	3.5	2	4 × 2.0	4	9.4	4.8	1	1.0	..	1.3	
16 ..	9.4	4.8	0	3 × 2.0	3	9.8	4.9	9	0.3			
17 ..	9.9	5.2	8	4 × 2.0	2	8.0	2.8	1	..	1.9	..	2.4
	8.0	2.8	2	8 × 2.0	4	9.0	4.4	2	1.0	..	1.9	
	9.0	4.7	..	....	..	10.5	5.9[4]					
						9.1	5.6					
18 ..	8.8	3.4	4	6 × 2.0	3	8.6	3.8	1	0.1	0.4		
						9.1	3.2[5]					

TABLE IX.—RESULT ON SERUM CALCIUM OF INJECTABLE PARATHYROID (GROUP 1).—(*Continued*)

Case.	Total calcium.	Diffusible calcium.	Number of days before injection.	Number of times injection was given × dose on each occasion.	Period of days consumed in injecting the entire amount.	Total calcium.	Diffusible calcium.	Days elapsed after injection before the calcium was reëstimated.	Total calcium.		Diffusible calcium.	
									Gain.	Loss.	Gain.	Loss.
19 ..	8.1	3.1	1	2	1	9.4	4.1	2	1.3	..	0.9	
						9.5	4.1[6]					
20 ..	8.8	3.5	83	3	1	8.9	3.7	10	..	..	0.2	
21 ..	10.9	6.5[7]										
	10.5	5.1	5	3 × 3.0	3	8.7	3.9	1	..	1.7	..	1.1
22 ..	8.7	4.2	4	6 × 3.0	6	9.6	4.2	9	0.9			
23 ..	9.8	4.1	1	7 × 3.0	7	9.4	4.8	2	..	0.3	0.6	
						10.4	4.2		..	..		
24 ..	10.1	4.3	3	1 × 2.0								
				3 × 3.0	4	10.1	5.0	3	..	..	0.7	

Total calcium: Thirty-one observations were made on these 24 cases. Twenty-one gained an average of 0.81 mg., with an average dose of 8.6 cc. of injectable parathyroid, spread over an average of 3.7 days, the dose multiplied by the number of occasions administered intramuscularly being indicated in the column designated "dose."

Ten lost an average of 0.93 mg., with an average dose of 9.5 cc. spread over an average of 3.3 days.

Diffusible calcium: Fifteen gained an average of 1.04 mg., with an average dose of 10.2 cc. spread over 3.5 days. Five lost an average of 1.12 mg., with an average dose of 10.6 cc. spread over three days.

The average total serum calcium of this group before treatment was 8.83 mg. per 100 cc.; the average diffusible calcium was 3.81 mg.

[1] Taken four days after injection.

[2] Taken eight days after injection.

[3] Calcium estimated at intervals of a week, with further treatment.

[4] Preceded by twelve injections of parathyroid, Group 2.

[5] Preceded by five injections of parathyroid, Group 2.

[6] Preceded by six injections of parathyroid, Group 2.

[7] This was a case of goiter, and after her injection of 3 cc. she had what she describes as having been accompanied with fever, restlessness and very severe headache. She took her own temperature however, and found it normal. The same thing occurred, but in less degree, after the second and third injections.

Two cubic centimeters of "carbonated" blood or cerebrospinal fluid are accurately pipetted into a small platinum crucible, evaporated to dryness, and then carefully incinerated over a low flame, at first heating the sides of the crucible, and then slowly extending the Bunsen burner flame downward. This incineration is completed with a stronger flame until all carbon is completely oxidized. The resulting ash is dissolved in 5 cc. of distilled water containing 5 drops of concentrated hydrochloric acid. If any "creeping" has taken place over the sides of the crucible this material is washed off with the solution into a small beaker, and the solution poured

back with washing into the crucible. The final solution in the crucible is evaporated to dryness on the water-bath, and the residue is treated with 8 cc. of water containing 6 drops of glacial acetic acid and 0.5 gm. of sodium acetate. The whole is now evaporated to from one-third to one-half its volume in a water-bath. It is now filtered through a small filter paper into a 15-cc. centrifuge tube,

TABLE X.—RESULT ON SERUM CALCIUM OF INJECTABLE PARATHYROID (GROUP 2).

Case.	Total calcium.	Diffusible calcium.	Number of days before injection.	Injectable parathyroid, cc.	Period of days consumed in injections.	Total calcium.	Diffusible calcium.	Days elapsed after injection before the calcium was re-examined.	Total calcium.		Diffusible calcium.	
									Gain.	Loss.	Gain.	Loss.
1 . .	9.5	5.2	1	6	18	10.5	6.7	1	1.0	..	1.5	
2 . .	9.0	4.7	13	12	24	10.5	5.9	5	1.5	..	1.1	
3 . .	9.4	4.2	11	6	18	10.1	4.5	49	0.7	..	0.2	
4 . .	11.1	3.0	22	6	10	9.7	4.5	5	..	1.3	1.4	
5 . .	8.1	4.1	6	3	4	9.3	3.8	1	1.1	..	..	0.2
6 . .	7.8	2.9	21	6	19	8.9	3.5	3	1.0	..	0.6	
7 . .	8.6	3.8	16	5	15	9.1	3.2	56	0.5	..	..	0.6
8 . .	9.5	2.0	16	6	18	9.6	5.1	3	0.1	..	3.1	
9 . .	9.3	4.4	4	6	15	12.6	6.9	62	3.3	..	2.4	
10 . .	9.4	4.1	18	6	27	9.5	4.1	3				
11 . .	7.5	3.3	3	6	15	8.5	5.7	15	0.8	..	2.4	
12 . .	9.4	3.7	5	6	21	9.5	6.7	9	0.1	..	3.0	
13 . .	9.5	6.7	16	3	11	9.1	4.7	24	..	0.4	..	2.0
14 . .	8.7	3.1	5	6	21	8.4	4.3	7	..	0.2	1.1	
15 . .	8.4	3.5	1	6	24	10.0	5.4	5	1.6	..	1.9	
16 . .	10.8	4.1	2	6	14	12.6	6.4	6	1.8	..	2.2	
17 . .	8.4	3.4	12	6	18	8.6	3.5	46	0.1	..		
18 . .	8.6	3.5	2	6	10	9.1	3.7	15	0.5	..	0.1	
19 . .	9.4	4.8	7	6	18	9.8	4.7	51	0.4			
20 . .	9.0	4.5	2	6	17	11.0	5.5	8	1.9	..	0.9	
21 . .	7.2	3.8	2	12	43	8.8	4.9	29	1.6	..	1.1	
22 . .	8.5	3.2	8	6	10	7.7	3.8	11	..	0.8	0.5	
23 . .	9.6	3.0	1	6	11	10.1	4.3	31	0.4	..	1.3	
24 . .	7.9	3.0	4	6	10	8.0	3.6	19	..	..	0.5	
25 . .	8.5	4.1	1	6	10	9.3	4.8	14	0.7	..	0.7	
26 . .	12.1	5.2	1	6	8	8.7	3.8	1	..	3.4	..	1.3
27 . .	7.8	2.5	6	6	15	10.6	5.1	1	2.8	..	2.6	

Of this group of 27 (26 cases, as 1 was examined twice), 22 gained an average of 1.04 mg. of total calcium, with an average dose of 6.8 cc. of injectable parathyroid, spread over an average of 17.5 days in 1-cc. doses injected intramuscularly every two to four days.

Five lost an average of 1.27 mg. of total calcium, with an average dose of 5.4 cc. spread over an average of twelve days.

In diffusible calcium 21 gained an average of 1.41 mg., with an average dose of 7.33 cc. spread over an average dose of 18.5 days. Five lost an average of 0.88 mg., with an average dose of 4.6 cc. spread over 11.2 days.

The average total serum calcium of this group before treatment was 9.03 mg. per 100 cc.; the average diffusible calcium was 3.88 mg.

and the crucible is washed three or four times with 1 to 2 cc. of distilled water containing a drop of glacial acetic acid. The washings are passed through the same filter paper into a porcelain dish, evaporated to a volume of 1 cc. and this is added to the centrifuge tube. An additional cubic centimeter of distilled water is added to wash the dish, and this is added to the tube. One cubic centimeter of concentrated ammonium oxalate solution is now added, and the subsequent procedure is that of Tisdall's modification of the Kramer-Tisdall method already described. The filter paper used in this work was that of Schleicher and Schull, No. 590, 5.5 cm.; HCl and HF washed. Blank tests failed to detect calcium.

The terms "ionized" and "ionic" calcium, as used by Vines[7] seems to us confusing. The proteins of blood serum combine with calcium and at the same time we have in this serum inorganic salts of the same metal. The organic combination seems to be in the form of suspensoids, so that when blood serum is dialyzed through collodion membranes, animal membranes, and the like, we will only obtain a certain percentage of the total serum calcium. What does Vines mean to call the nondialyzable calcium of the serum adsorbed calcium ions?

The terminology becomes serious when applied by Scott, as one gathers that what we call the "total serum calcium," he refers to as "ionic calcium." As ionic calcium should all be diffusible, we feel confused as to the interpretation of his results. Attention is invited to the individual instability of serum calcium and to the astonishingly stable statistical average of a series of cases. The very generally accepted dictum that the calcium concentration of blood is one of the most stable quantities in the human body should be interpreted in this sense only, for from our figures the range of calcium values for the individual shows serum calcium to be fully as unstable as the formed elements of the blood and the hemoglobin. Innumerable instances of a very low diffusible and a normal total calcium in blood serum are seen in all of our series. In correspondence with one scientific center, we were told that the diffusible calcium was never estimated by them because it was always 50 per cent of the total. This seems to be more or less true for the statistical average, as seen in Table VIII, although our average is 44.8 per cent for the pathologic series, but the individual variability of diffusible calcium, at least, seems to be a very real thing, and may later prove to be a most important factor in these problems. In fact, we have already seen the tendency toward low values for diffusible serum calcium in high grades of malnutrition.

Summary. In short, low-calcium values in blood serum are to us indicative of serious malnutrition rather than of specific disease. It seems better to state this condition in terms of parathyroid deficiency rather than in terms of calcium deficiency, particularly as it is rather the diffusible than the total calcium that is affected.

So far as we have gone, the calcium index seems to reflect strongly on the nutritional state of a group, all the elements of which are subjected to the same general conditions. We agree with Scott that calcium deficiency occurs in sprue, but it is very evident to us that in other diseases, and particularly in pure malnutrition in the tropics, it also exists, at times to an even greater degree. Most of all, it is not by any means constant. May we not imagine that persons subjected to sprue, or other source of malnutrition, have a varying degree of vitality, of histologic perfection, of functional activity of their parathyroids? Perhaps heredity contributes its part in furnishing a sound or a flimsy glandular apparatus.

In closing this paper it seems opportune that the medical representative in this study should state as clearly as possible his position regarding the nature of sprue. Among the very first papers published by him in 1915, concomitantly with the announcement of the presence of Monilia psilosis in these cases, and from that time to this he has felt that sprue is developed usually upon a background of nutritional unbalance and subsequent glandular insufficiency.[1, 8, 9, 10, 11, 12, 13, 14] He conceives sprue in the tropics to be a congenor of thrush in the north, as Monilia psilosis is a congenor of Monilia albicans. Both clinical entities, as such recognized, and both receiving names based on the clinical distinctness of their respective pictures, are usually infections upon a state of nutritional unbalance; in the case of sprue, upon a condition of chronic digestive incompetence; in the case of thrush, upon the marasmus of infants, of the senile and of the wasted subjects of chronic disease. At times, without the previous state of malnutrition, both may be produced by sheer force of infection.

While no attempt is made in this paper to go into details concerning the part played by Monilia psilosis in sprue, it is pertinent to say that of the 101 cases of nutritional unbalance reported in this paper, 38 had cultures made from their feces and 2 were positive for Monilia psilosis, or 5.3 per cent, while of the 55 cases of sprue, 35 were positive for Monilia psilosis, 13 are as yet unclassified but positive for Monilia of doubtful species, and 6 are negative for all fungi, a percentage of positives of 63.6 per cent. As throwing further light upon the relative presence of Monilia psilosis in healthy persons, the feces of 178 supposedly healthy boys in the Boys' Charity School of San Juan were cultured and in 7 Monilia psilosis was found (1 not typical, and therefore doubtful), a percentage of positives of 3.9.

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REVIEWS.

A MANUAL OF CLINICAL LABORATORY METHODS. By CLYDE LOTTRIDGE CUMMER, PH.B., M.D., Associate Professor of Clinical Pathology, School of Medicine, Western Reserve University, Cleveland. Second edition, thoroughly revised. Pp. 547; 181 illustrations. Philadelphia and New York: Lea & Febiger, 1926. Price, $6.50.

IN this edition the chapter on blood has been subdivided into five chapters; new variations of the Wassermann reaction and new blood chemical methods described. New sections on cutaneous reactions and basal metabolism (by M. A. Blankenhorn) have been added.

To confine attention to one section, exception must be taken to the depiction and description of the large mononuclear leukocytes, which confound a confused situation by placing them indistinguishably close to the large form of lymphocyte. Better methods for the oxydase stain might be included, and one is astonished to see no mention of the much-talked of icterus index or van den Bergh's test. Fragility of leukocytes, motility of leukocytes and some simplification of the Arneth count might with propriety have been included. Nevertheless as such books go—and there are plenty of them—this work is entitled to take a worthy place among the up-to-date medium-sized manuals on the subject. E. K.

INDIVIDUAL GYMNASTICS: A HANDBOOK OF CORRECTIVE AND REMEDIAL GYMNASTICS. By LILLIAN CURTIS DREW, Director of Department of Corrective Gymnastics, Central Branch, Y. W. C. A., New York City. Third edition, thoroughly revised. Pp. 276. Philadelphia and New York: Lea & Febiger, 1926. Price, $2.25.

THE appearance of a new and revised edition of this work on individual gymnastics is an indication of the increased place this book is filling in the library of the progressive physician, as well as that of the teacher of physical education.

The author goes at her subject without waste of words and gives

clear and brief directions for the exercises described. Most of them are arranged in prescription form, easily understood. For example: The exercises for the correction of flat feet are arranged under the head of Walking, Sitting and Passive Exercises, and end with Competitive Games, like lifting marbles with the toes and dropping them into a basket. The importance of mechanical correction in scoliosis and flat feet is noted and briefly described, showing that the author is conversant with these problems from every side. R. McK.

DISEASES OF THE HEART. By SIR JAMES MACKENZIE, F.R.S., M.D., F.R.C.P., Director, St. Andrew's Institute for Clinical Research; Consulting Physician to the London Hospital; Consulting Physician to H. M. the King of Scotland. Fourth edition. Pp. 496; 342 illustrations. Oxford University Press, 1925. Price, 30 shillings.

THIS edition, completed within a few weeks of the author's death, appears twelve years after the third, though several reprintings and revisions have occurred in the *interim*. During this period Mackenzie became firmly convinced that "the conception of research which is dominant today is inadequate for the solution of many medical problems," and often leads into relatively sterile by-paths. He vigorously maintained that we must endeavor to learn the nature of the phenomena of ill-health and that recognition of factors concerned in producing symptoms may be obtained not from speculations on colloids, electrons and the like, but from proper study of living functioning cells of the body. One manifestation of this concept is the admirable St. Andrew's Institute for Clinical Research; the other is Mackenzie's individual literary output—astonishing for an elderly man already stricken with angina—to be found in the complete revisions of the book under review and of *Symptoms and their Interpretation;* in numerous articles for the medical and lay press; in the Reports of St. Andrew's Institute and his book, *Angina Pectoris* (see AM. JOUR. MED. SCI., 1925, **169,** 595). A summary of Mackenzie's views can be found in a letter written shortly before his death and published in the *London Times* of February 12, 1925, under the title "The Science of Medicine—Basic Principles of Research."

This edition is certainly entirely rewritten. Not only are the Preface, Introduction and most of the first thirteen chapters largely devoted to an exposition of the author's newer views, but these also infiltrate the more strictly cardiac chapters, which have been thoroughly shuffled and often disguised. Some eighteen chapters on the anatomy and physiology of the heart (with emphasis on the genetic system) are followed, by no means uninterruptedly, by

thirty-six on various cardiac disorders, the book terminating with various chapters on methods of examination, venous pulse and enlargement of the liver. Despite the confusion of this rather bewildering arrangement, this book challenges attention even more than previous editions and will repay the close study of all students of medicine as well as of cardiologists. E. K.

A Companion to Manuals of Practical Anatomy. By E. B. Jamieson, M.D., Senior Demonstrator and Lecturer on Anatomy, University of Edinburgh. Second edition. Pp. 558. New York: William Wood & Co., 1925.

This little book, which went through six impressions before the second edition was published, has long been looked for by demonstrators of anatomy. The general arrangement is the same as in the first edition. Brief descriptions of the autonomic nervous system, the paraganglia and the bone marrow have been added. The sections on lymph glands, ductless glands and the nervous system have been largely rewritten. The Basle nomenclature has been employed, within those places where this nomenclature varies widely from the old terminology the latter has been inserted in brackets. This book should not be used as a text in itself, but is to be used by those who have "already gone over the ground, with the aid of a dissecting manual." It is accurate, concise and easily portable. The reviewer considers it the best compendium available today. I. R.

Operating Room Procedure (for Nurses and Interns). By Henry C. Falk, M.D., Assistant Attending Surgeon to the French Hospital; Assistant Attending Gynecologist to the Harlem Hospital; Instructor in Surgery at New York University and Bellevue Medical College; with a foreword by Eugene H. Pool, M.D. Pp. 385; 275 illustrations. New York: G. P. Putnam's Sons, 1925.

This book, which was based upon a course of lectures delivered to the operating-room nurses at the French Hospital of New York City, will be welcomed by operating-room nurses throughout the country. The first part deals with the preparations of the accessories used in and about the operating room. The second part considers the specific preparation of the operating room for the various operations most commonly performed in the scope of a general surgical service. The technique of both the preliminary and the operative procedures is given step by step. The book is well arranged and is written in a style that makes it readable. I. R.

ELEMENTARY MORPHOLOGY AND PHYSIOLOGY FOR MEDICAL STUDENTS. By J. H. WOODGER, B.Sc., Middlesex Hospital Medical School; Reader in Biology in the University of London. Pp. 528; 255 figures. London: Humphrey Milford, Oxford University Press, 1924.

THIS is a college zoölogy textbook written along rather original lines. While it is intended for the premedical student, it is also well adapted for general zoölogical teaching. The author believes there is insufficient correlation between the biological facts taught and the future needs of the student, so he lays emphasis upon the interpretation of the morphological data, and thus encourages the student to think about what he is learning. The main forms described are amœba, paramœcium and euglena of the protozoa, hydra and obelia, distomum and tænia, lumbricus, amphioxus, scyllium, rana and lepus of the metazoa. There are chapters on ontogeny, phylogeny, comparative physiology, interpretation of biology and animal behavior or psychology. As an epilogue, there is a short account of the method of science, and there are two pages of references for collateral reading. It is evidently a book for the serious student, and is to be highly recommended. W. A.

PARASITOLOGY (FOR MEDICAL STUDENTS). By A. MILLS KENNEDY, M.D. (GLASGOW), Professor of Medicine, University of Wales, and Director of the Medical Unit of the Welsh National School of Medicine. Pp. 142; 1 color plate and 61 illustrations. London and New York: Humphrey Milford, Oxford University Press, 1925.

THE author presents in this book a brief account of those parasites which are of practical importance from the point of view of the practising physician. The differential characters and life history of these parasites, together with a discussion of the diagnosis, prophylaxis and treatment of the diseases caused by them, are well presented in compact form. The book is made up of chapters on insects and aracnoids, tapeworms, flukes, round worms, protozoa and spirochetes and fungi. It represents a useful compend of practical information for the medical practitioner. J. S.

MIDDLE AGE AND OLD AGE. By LEONARD WILLIAMS, M.D. Pp. 296; 1 illustration. London: Oxford University Press, 1925.

STARTING from the premise that man should live one hundred and twenty years, and should not commence to decline until the

age of eighty, the author points out the reasons why this is not achieved and the means by which it might be. Pretty much everything is wrong today—our diet, habits, water closets, our neglect of venesection and fasting, and so forth. The views of Lane and of Voronoff are accepted, and the author is even tempted to see good in Abram's electrotonic reactions. From a hodge podge of quotations from sources good, bad and indifferent, a discursive thesis is woven. Apparently in order to live one hundred and twenty years one must devote oneself from birth, or even earlier, to that end. The book is published in the usual excellent but monotonous style of the Oxford publications. O. P.

THE ART AND PRACTICE OF MEDICAL WRITING. By GEORGE H. SIMMONS, M.D., Editor and General Manager Emeritus, America Medical Association; and MORRIS FISHBEIN, M.D., Editor, The Journal of the American Medical Association. Pp. 163; 23 illustrations. Chicago: American Medical Association, 1925.

ANYONE who could ensure that this booklet would be perused by every prospective author of a medical paper would certainly receive the blessings of all medical editors and publishers. He would also have done more than his bit in helping to remove the opprobrium that alas justly falls on many American medical writers for their lack of clearness, ease and other details that go to make up a good style. An expansion of *Suggestions to Medical Authors*, the book not only tells the aspirant how properly to write and illustrate a scientific paper, but furnishes valuable bibliographic information on such topics as lists of medical journals, both current and obsolete, proof-reading conventions, desirable abbreviations and so forth. It should be given widespread circulation by those interested in medical journalism from all its aspects. E. K.

INTRAVENOUS THERAPY. By WALTON FORREST DUTTON, M.D., Director, Medical Research Laboratories, Amarillo, Texas. Second edition. Pp. 594; 64 illustrations. Philadelphia: F. A. Davis Company, 1925. Price, $6.00.

THE general plan of this work is to present facts and experience concerning the use of intravenous measures under two main heads—technique and actual therapy—thus dividing the book into two almost distinct sections.

In the first portion the author begins with the history of the technique of intravenous therapy and ends with its most up-to-

date phase—intravenous anesthesia. In every one of these first twelve chapters methods are carefully and clearly described, essential and helpful details are well brought out, and in every particular it is evident that the reader is gleaning profit from the pen of an operator long experienced and well versed in the field which he is describing. The diagrams and photographs are also to the point, and nothing could be more ingenious nor simple than the author's portable apparatus for citrated blood transfusion.

Concerning the portion of the book dealing with detailed intravenous therapy, serious objection must be made to its unwarranted length. It is a foregone conclusion that a physician who wishes to learn about intravenous medication for a certain disease is *ipso facto* already well acquainted with the general diagnosis, symptomatology and usual treatment of that disease. Therefore, space given to these items in a manual of intravenous therapy is a tautological waste of print and time. The actual intravenous therapy recommended in each disease seems to be in agreement with the most modern thought. C. L.

AN INTRODUCTION TO OBJECTIVE PSYCHOPATHOLOGY. By G. V. HAMILTON, M.D. Director of Psychobiological Research, Bureau of Social Hygiene, Inc., New York City. Pp. 353. St. Louis: C. V. Mosby Company, 1925. Price, $5.00.

HALF of this book is taken up with the histories of 200 cases studied by the author in one little community. It is rather refreshing to find that, while "the book is essentially a psychopathologist's account of his studies and interpretations of various modes of human and animal behavior," there is much emphasis laid on the physical factors in the production of nervous conditions. It is also exceedingly refreshing to read of certain failure in therapy of the neuroses with the author's methods as with other procedures. The reviewer feels that many of the cases should have been gone into more thoroughly. The second half of the book is a general consideration of the results and findings in the 200 cases, under five headings: Psychopathology, a Part of Medicine; Neural Morphology; Neural Physiology; Endocrinology and Behaviorism.

The reviewer feels that the book is worth while for all students of nervous disorders, but is not to be recommended to the lay people, as is intended by the author, since he himself admits "that this has required the formulation of research methods which at best cannot be regarded as other than provisional, and greatly in need of refinement." N. W.

BOOKS RECEIVED

LEAD POISONING. By Joseph C. Aub, Lawrence T. Fairhill, A. S. Minot and Paul Reznikoff. Medicine Monographs, Vol. VII. Pp. 265; 35 illustrations. Baltimore: Williams & Wilkins Co., 1926. Price, $4.00.

TEXTBOOK OF PHARMACEUTICAL CHEMISTRY. By Arthur Owen Bentley, Ph.C. and John Edmund Driver, M.Sc. Pp. 456. New York: Oxford University Press, American Branch, 1926. Price, $6.00.

RECENT ADVANCES IN OBSTETRICS AND GYNECOLOGY. By Aleck W. Bourne, B.A., M.B., B.Ch., F.R.C.S. Pp. 344; 58 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $3.50.

INTESTINAL TUBERCULOSIS. By Lawrason Brown, M.D. and Homer L. Sampson. Pp. 304; 112 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $4.00.

A COLLEGE TEXTBOOK OF PHYSIOLOGY. By Arthur Dermont Bush, B.S., M.D. Pp. 331; 101 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $3.50.

THE BIOLOGY OF THE PROTOZOA. By Gary N. Calkins, Ph.D. Pp. 623; 238 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $7.50.

A MANUAL OF CLINICAL LABORATORY METHODS. By Clyde Lottridge Cummer, Ph.B., M.D. Pp. 547; 181 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $6.50.

RECENT ADVANCES IN PHYSIOLOGY. By C. Lovatt Evans. Pp. 364; 69 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926.

ULTRA-VIOLET RAYS IN THE TREATMENT OF DISEASE. By Percy Hall, M.R.C.S. (Eng.), L.R.C.P. (Lond.). Pp. 110; 20 illustrations. St. Louis: C. V. Mosby Company, 1924. Price, $3.75.

MUSCULAR ACTIVITY. By Archibald Vivian Hill, D.Sc., F.R.S. Pp. 115; 47 illustrations. Baltimore: Williams & Wilkins Co., 1926. Price, $2.75.

SCOLIOSIS. By Samuel Kleinberg, M.D., F.A.C.S. Pp. 311; 140 illustrations. New York: Paul B. Hoeber, 1926. Price, $6.00.

PSYCHOANALYSIS AND BEYOND PSYCHOANALYSIS. By Leonard L. Landis, M.D. Pp. 212; 1 illustration. New York: American Association of Independent Physicians, 1926.

SECRETIONS OF THE SEX GLANDS. By Alexander Lipschütz, M.D. Pp. 513; 140 illustrations. Baltimore, Williams & Wilkins Co., 1924. Price, $6.00.

LIGHT AND HEALTH. By M. Luckiesh and A. J. Pacini. Pp. 302; 31 illustrations. Baltimore, William & Wilkins Co., 1926. Price, $5.00.

PROGRESS

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The Value of the Roentgen Ray on Determining the Cause of Aortic Regurgitation.—LEDBETTER, HOLMES and WHITE (*Am. Heart Jour.*, 1925, **1**, 196) report a series of 34 cases of aortic regurgitation including 13 syphilitic, 6 arteriosclerotic and hypertensive, 5 rheumatic, and 10 rheumatic plus mitral valve involvement. In rheumatic aortic regurgitation without other valvular disease the aortic shadow is normal in all views. In cases of syphilitic origin the Roentgen ray findings to be looked for are: (1) An increase in the supracardiac shadow which is usually found just above the heart shadow, to the right of the sternum in the region of the aortic valve; (2) abnormal pulsations in the region of the ascending aorta; (3) a cone-shaped supracardiac shadow; (4) a flattened aortic knob, (5) pyramid-like shadows extending upward from the aorta in the region of the innominate and subclavian arteries, and (6) changes in the appearance of the heart shadow—either a moderate general enlargement accompanied by a poorly defined left ventricle and flabby beat, or a marked enlargement of the left side of the heart, with a blunt apex and horizontal position. In arteriosclerosis with aortic regurgitation the enlargement of the heart may not differ from that of the syphilitic type, but the aorta is tortuous rather than dilated, so that in the oblique view the actual diameter of the ascending aorta is not increased, although there may be marked increase in the supracardiac dullness in the antero-posterior view. The aortic knob is prominent, not flattened as in syphilitic aortitis, and calcified plaques may be visible.

The Therapeutic Relationships of Digitalis and Strophanthus.—CORNWALL (*Med. J. and Rec.*, 1925, **121**, 752; 1925, **122**, 39) writes that the physiological action of strophanthus differs radically from that of digitalis. He states that if digitalis stimulates the vagus but does not increase tonicity and contractility, while strophanthus does not stimulate the vagus but does increase tonicity and contractility, the difference in the action of the two drugs would seem to be radical. Lewis, Mackenzie and Wenckebach are quoted as stating that the chief action of digitalis is to slow the heart and that there is little if any effect on the myocardium. The therapeutic indications of strophanthus are more extensive than those of digitalis and include all conditions where heart failure is due to or complicated by intrinsic weakness of the heart muscle. In dilatation from any cause where the prognosis is bad, strophanthus is more effective than digitalis. Digitalis has an almost specific action in the treatment of heart failure associated with auricular fibrillation. It is thus a regulator of the heart's action, that is, of the rhythm and rate of the heart's action, while strophanthus is a direct heart stimulant. The dose of strophanthus preparations, preferably strophanthin, ranges from grain 1 to 1000 to grain 1 to 250 every four hours and a full dose is grain 1 to 500 every four hours. In emergencies a single dose of grain 1 to 100 may be given intravenously or intramuscularly, after which no more should be given for twenty-four hours. Great care should be taken in giving strophanthus after a strong course of digitalis, as it can precipitate digitalis poisoning; but if given before a course of digitalis, it is not likely to prove thus dangerous, being quickly eliminated or destroyed.

Effect of Parathyroid Extract and Liver Extract on the Hypertension Produced by Guanidine Compounds.—RALPH H. MAJOR and C. R. BUIKSTRA (*Bull. Johns Hopkins Hosp.*, 1925, **37**, 392) studied the influence of extracts of the parathyroids and of the liver upon the duration of the four or five hour elevation of blood-pressure produced by the guanidine bases and recently described by Major. The parathyroid extract was used because of its possible relation to idiopathic tetany and tetany parathyreopriva. The intravenous injection of 5 to 10 cc. of extracts prepared by the methods of Hanson and of Collip had no effect upon the normal blood-pressure of a dog. In 10 experiments the injection of 1 to 5 cc. samples of parathyroid extracts five minutes after the injection of methyl-guanidine sulphate (0.1 gm. per kilo) promptly produced a gradual fall of the elevated blood-pressure which, in the tracings shown, reached normal in about twenty-five minutes. This effect could not be ascribed to the hydrochloric acid present in the extracts used, as more than ten times the amount of acid present was required to produce a lowering of the guanidine-elevated blood-pressure. Similarly, liver extracts, prepared with hydrochloric acid, produced a prompt fall of the elevated blood-pressure to normal. Liver extracts had the same effect upon normal blood-pressure as does amyl nitrite, but, while the latter caused only a transient drop in the high blood-pressure due to methyl-guanidine, liver extracts reduced this promptly and permanently. Seven tracings were given.

SURGERY

UNDER THE CHARGE OF

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Primary Carcinoma of Lung.—BRUNN (*Arch. Surg.*, 1926, **12**, 406) says that primary carcinoma of the lung is more prevalent than heretofore supposed. The symptoms may be variable and diagnosis thereby delayed. The roentgenologic findings are not uniform; they depend on the type of tumor, its location, mode of growth and such secondary processes as may arise in the lung. Diagnosis will depend on a study of the growth in correlation with the symptoms. More cases should and can be brought to surgery in the operable stage by early diagnosis or by exploratory operation. The pituitary gland should be carefully examined at postmortem, in cases of pulmonary osteoarthropathy. Surgery offers some hope to those hopeless sufferers either in relief of pain, amelioration of symptoms or perhaps in a cure.

Carcinoma of the Male Breast.—JUDD and MORSE (*Surg., Gynec. and Obstet.*, 1926, **42**, 15) state that it is probable that carcinoma of the male breast in most instances is a highly malignant type of neoplasm. The results of radical operation for cancer of the breast are not as satisfactory in males as in females, very likely because in the former the tumors are generally of a higher degree of malignancy. Tumors in the male breast should receive immediate radical operative treatment. Good results are obtainable only by radical operation before glandular or other metastatic lesions occur. Roentgenoglogic treatment postoperatively does not seem to have arrested the progress of the disease to any appreciable extent in this series of cases.

Systematic Diagnosis in Backache.—WENTWORTH (*J. Bone and Joint Dis.*, 1926, **8**, 137) says that chief consideration is given to differential diagnosis of four types of traumatic back: sacro-iliac strain, sacro-iliac subluxation, lumbo-sacral strain, fractures and dislocations in the lumbo-sacral region; to static backs often in those physically unfit for the overstress of life and to osteo-arthritic backs. Preconceived ideas of pathology must be eliminated from the process of making a diagnosis. Elimination of guesswork or what the lawyer ironically calls opinion is the purpose in setting forth the method of diagnosis. Opinion must give way to systematic diagnosis. The many pathologies may give rise to similar complaints of pain, weakness and limited motion, but systematic search reveals discriminating objective evidence of many distinct lesions. Only a very few cases leave injury out of the history. As a rule histories of radiating pain are inaccurate and of very little

differentiating value as compared with subjective location of constant pain. Sciatic pain is not necessarily sciatica but may be. Exaggeration is as common as malingering is rare. Spinal deviations are of little or no differentiating value. Posture, including the feet, is an important element in static backs and static sacro-iliac strains. The flat lumbar spine is common in sacro-iliac subluxation. The age factor must always be borne in mind when considering range of spinal flexibility. Pain in thigh hyperextension has no differentiating value. Audible clicks are not pathognomonic of sacro-iliac relaxation. Reduction of subluxation is a definite scientific procedure, evident to both patient and surgeon when obtained. Altered reflexes, muscle atrophies and paralyses, localized clonic contractions; trophic changes, areas of decreased or altered tactile sensibility and hyperalgesia are important in neuritis, perineuritis, radiculitis and nerve injury, but not in bone and joint lesions. Areas of localized tenderness are of great value. Cases of traumatic strain limited to lumbo-sacral or to sacro-iliac ligaments are rare. In most cases of traumatic strain both sets of ligaments are involved.

Statistical Study of Radiation Therapy in Carcinoma of the Breast.—PFAHLER and WIDMANN (*Am. J. Roentgenol. and Radium Therap.*, 1925, **14**, 550) say that the radiologist has the same factors to consider as the surgeon as expressed by Ewing who says, "In mammary cancer, surgery meets with more peculiar difficulties and uncertainties than with almost any other form of the disease. The anatomical types of the disease are so numerous, the variations in the clinical course so wide, the paths of dissemination so free and diverse, the difficulties of determining the actual conditions so complex, and the sacrifice of tissue so great, as to render impossible in a majority of cases a reasonably accurate adjustment of means to ends." These same factors complicate the classification of mammary cancer for the radiologist, so that comparative statistics must take into account not only the duration of the disease before and after operation, but also the extent of involvement and even then conclusions at best can be only relative. Radiation has not only proven its value, but its necessity in mammary cancer.

The Significance of Vital Capacity in Intrathoracic Therapy.—YATES (*Arch. Surg.*, 1926, **12**, 251) state that vital capacity, the largest expiration following the deepest inspiration varies with age and sex, height and weight, health and disease and often periods of rest and exertion. Estimations of vital capacity are helpful in diagnosis, in prognosis, in determining the effects of treatment and in measuring ultimate results as they record the effectiveness of the basic function, and external respiration. Protection of the structure and of the activities of the structures that establish and control external respiration, so that vital capacity is kept at the highest level permitted by circumstances is the guide to effective treatment of intrathoracic diseases. Resistance, defense, growth and repair of intrathoracic structures, as well as of the entire organism, are commensurate with vital capacity. Application of the principles suggested in treatment of patients suffering from pleuropulmonary injuries and diseases should lead to more complete recoveries than are otherwise obtainable.

PEDIATRICS

UNDER THE CHARGE OF

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Gastric Acidity in Syphilitic Children.—DORNE, BRAMS and TUMPEER (*J. Am. Med. Assn.*, 1926, **86**, 267) state that the findings of Neugebauer were substantiated in his observations on children. Viewed from all angles, the data demonstrate lowered acidity in the gastric contents of syphilitic children. This is apparent from a comparison of the average values of a group of controls and a group of children with syphilis. It is further borne out in separating the individual cases of both groups, and comparing the relative proportions of cases above and below the average of each group. The same facts are disclosed when the series is split into age groups. Separation of individual cases in the manner described more accurately and more completely expresses the facts. Data concerning conditions in the unknown must be related in terms of the known. Neugebauer's conclusion, that 80 per cent of syphilitic persons show hypoacidity, is misleading, as it implies that hypoacidity in itself is abnormal, and that in individuals otherwise normal do not manifest hypoacidity. By virtue of the definition of average, there must be a certain proportion of normal individuals with values above the average and a certain proportion below this average. Therefore, Neugebauer's 80 per cent must be related to the percentage of normal individuals who show hypoacidity. The term approximately is used throughout first because the proportions are expressed in round numbers for convenience, and second the results in a small number of cases, although carefully controlled, are approximate for the situation in general. In this work they established the point that syphilitic children show a hypoacidity of the gastric contents.

Intracranial Hemorrhage in the Newborn.—SHARPE and MACLAIRE (*J. Am. Med. Assn.*, 1926, **86**, 332), in their series of 500 consecutive newborn babies, on whom the lumbar punctures were performed within from twelve to twenty-four hours after birth, it was seen that in 45 babies there was found bloody and blood-tinged cerebrospinal fluid. This was 9 per cent of the entire series. One baby died before the lumbar puncture was done, but it was done fifteen minutes after death. In this case at necropsy there was revealed an extensive intracranial hemorrhage with bloody spinal fluid. It must also be remembered that as many as 50 babies, or 10 per cent of the entire series, were not tapped; in 36 a dry tap was recorded; in 14 the test was not performed as 7 babies were in severe shock and 7 premature babies were in poor condition. In making the test, if bloody, blood-tinged or yellow, and straw-colored cerebrospinal fluid was disclosed, then another immediate confirmatory puncture was made one interspace higher, merely to prove or disprove the presence of the blood in the

first test. In the bloody cases another test was made within a period of twenty-four hours, and cerebrospinal fluid was drained of an amount not to lower the pressure below the normal from 4 to 6 mm. of mercury. These daily tests were repeated until the fluid became clear and normal pressure. As many as seven punctures of drainage were necessary in several cases, and yet the average number was slightly over 3. There were 3 deaths in this series of newborn babies upon whom a lumbar puncture was done and which revealed blood in the cerebrospinal fluid. Postmortem examinations disclosed a large ventricular hemorrhage in the first, extensive subcortical hemorrhage and cerebral edema in the second and large subcortical, basal, subtentorial and spinal hemorrhage in the third baby. Their common signs were stupor and refusal to nurse; convulsive twitches in the third case only. The clinical signs suggestive of an intracranial lesion have been most meager, and were usually apparently lacking. Only 73 babies exhibited clinical signs, and their order of frequency was as follows: Muscular twitches of the hands and fingers in 15, in only 5 of whom was the cerebrospinal fluid bloody; muscular twitches of the feet and toes in 11, of whom 4 had bloody fluid; prolonged cyanosis in 9; in only 2 was blood found in the fluid; poor nursing in 7, of whom 2 had blood in the spinal fluid. The presence of rigidity in 2 cases was very significant, in that both babies had bloody fluid; respiratory difficulties in a mild degree, such as slightly irregular and labored breathing, in 14 babies, of whom only 2 had bloody fluid, and other signs such as frothing at the mouth in 1 baby having yellow fluid, and epistaxis in 2, of whom 1 had bloody fluid. In 73 cases having clinical signs suggestive of a possible intracranial lesion, only 25 had blood in the spinal fluid and 8 were not recorded. The intradural pressure in these 73 cases having clinical signs was increased in 30, normal in 28 and diminished in 6. The anterior fontanel was flush in 24, bulging in 15 and depressed in 25. The blood clotting time was normal in 35, prolonged in 6 and decreased in 10. The mother's blood Wassermann was positive in 6. From these figures, it can be seen that the possible signs of an acute intracranial hemorrhage of mild degree at the time of birth are inconstant and apparently in many cases entirely lacking. In the 45 babies having blood in the spinal fluid in varying degree, 33 were males and 22 were first children, only 4 being premature. The labor was normal, left occipitoanterior and right occipitoanterior in 24; prolonged in 7; precipitate in 3; low forceps in 3, 1 of which followed a prolonged labor; medium forceps in 4; breech extraction in 2; version with breech extraction in 1; a face presentation in 1. The anterior fontanel was flush in 20, tense and bulging in 11 and depressed in 14. The cerebrospinal fluid was bloody in 22, blood-tinged in 9 and yellow in 14. The blood clotting time was within normal limits for each one, one of the babies having blood in the cerebrospinal fluid varying from three to ten minutes, the average being five. The intradural pressure averaged 10 mm. Seventeen babies became jaundiced, in only 2 of whom was the cerebrospinal fluid bloody and under 8 mm. and 14 mm. of pressure respectively; the blood clotting time was four and a half and five and a half minutes respectively; five in 1 and three lumbar punctures in the other were necessary to obtain clear fluid. The Wassermann reaction was positive in both mother and child in only 1 case, in which

there was free blood in the spinal fluid; it was 4+ in 2 mothers, but negative in their babies, 1+ in 2 mothers, but negative in their babies; 1+ in 1 baby, but negative in its mother. The early recognition and the appropriate treatment of the acute conditions of intracranial hemorrhage in the newborn may thus lessen that large chronic group of physically impaired and mentally retarded children.

OBSTETRICS

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A Brief Review of the Maternity Work in Rotunda Lying-in Hospital, Dublin Ireland, 1923–1924.—As the Rotunda teaching and methods are world-wide and famous, and as many consider the Rotunda one of the greatest schools and the seat of obstetric learning, a short summary of the maternity cases taken from the *Irish Journal of Medical Science* and the summary published in the *Journal of the American Medical Association* for December, 1925, may be of interest. G. FITZGIBBON, R. M. CORBETT and N. M. FALKINER (*Irish J. Med. Sci.*, 1925, p. 337; *Rotunda Lying-in Hospital Report for* 1923–1924, p. 337). 1973 patients were admitted to the Rotunda Lying-in Hospital and 1703 were confined. Normal vertex was the presentation in 1498 deliveries. This includes all occipitoposterior positions which underwent normal rotation. Eighteen vertex presentations were finally delivered as persistent occipitoposterior. Face presentation, excluding anencephalus, occurred eight times. Transverse presentation, excluding multiple pregnancies occurred in 5 cases. Compound presentation occurred four times. Breech was the primary presentation in 51 cases, besides occurring in one of twins on nine occasions. There were 20 cases of twin pregnancies and 17 cases of prolapse of the cord. Forceps were applied for the delivery of 101 cases, 78 primiparas and 23 multiparas. Version was performed 31 times. In 4 cases the fetus was broken up to effect delivery. Persistent primary uterine inertia was present in 8 cases. There was only 1 case of definite contraction ring dystocia. Induction of labor was performed thirty times and induction of abortion or miscarriage seven times. Eight cases of accidental hemorrhage occurred. There were 12 cases of placenta previa, 7 cases of postpartem hemorrhage and 3 cases of rupture of the uterus. The placenta had to be removed manually nineteen times. There were 163 patients with external measurements considerably under normal. Internal pelvimetry was done only once, as dependence was placed far more on the application of the head to the pelvic brim, as made out under anesthesia and by noting the progress of labor, than on the actual

dimensions of the pelvis. Delivery was effected by Cesarean section nineteen times, 6 patients had sections done previously, in 2 patients it was the third section. One patient was delivered by pubiotomy after thirty-six hours in labor, the head being impacted in the brim. In 16 cases treatment was by induction of labor, eleven times for definite contraction of the pelvis and five for disproportion owing to the large size of the fetus. In 220 patients the urine was found to contain a marked amount of albumin. In 3 cases hyperemesis occurred. There were 10 deaths in the intern department, the causes were: Sepsis, rupture of Cesarean scar, rupture of uterus during evacuation, and hemorrhage in a full-term ectopic pregnancy, the patient dying just after laparotomy. One patient of cardiac failure from myocarditis. In the extern department there were 11 deaths, making in the whole maternity department service, 21 deaths. Twelve patients were admitted on account of pain and were found to have pyelitis. There were 3 cases of hydatid mole; 3 cases of multiple fibroids of large size with pregnancy; 1 case of chorea; 4 cases of mania and 1 of marked mental derangement for a few days after eclampsia; 1 case each of herpes, gall stones, appendicitis, anemia, erysipelas and thrombosis of the saphenous vein.

The Shortage of Birth Reports.—The birth rate in Philadelphia is decreasing. In the report of the Department of Health (*Monthly Bulletin of Department of Health, City of Philadelphia*, 1925, **10**, 166) it is reported that in the year 1925 there were 2000 less births reported during that year than in 1924. Granting a large proportion of the decrease in the births may be due to unreported returns of the physician or midwives, attention is called to the fact that we are actually experiencing a true decline of the birth rate in this city. In 1921 the birth rate was 23.15 per 1000 population and in 1924 21.2, thus in a period of three years there has been a decline of 2000 births, although there should have been under normal conditions an increase of population and an actual increase in the total number of babies born. If this present loss of infant population continues as it has in the past few years Philadelphia's birth rate would be zero in 1985.

Reporting of Maternal Deaths.—The EDITOR (Current Comment Editorials, *J. Am. Med. Assn.*, 1926, **86**, 421) calls attention to the fact that in 1924 the maternal mortality per 100,000 white mothers between the ages of fifteen and forty-four years was 59.1; of these, 22.5 died of puerperal septicemia. The present status of puerperal septicemia is summarized. Attention is called to the fact that the attending physician may be unjustifiably held responsible for the death, and courage on his part is required to accurately report the cause of death.

Placenta Previa.—COSTA and LANDA (*Bol. d. Soc. d. obstet. y ginec.*, Buenos Aires, 1926, **4**, 378) studied 203 cases of placenta previa at the the Woman's Clinic, 1914 to 1923. These cases formed 1.04 per cent of the total 19,450 pregnant women. Their mortality was 5.4 per cent, omitting morbid cases. The death rate of the viable children, 47 per cent, emphasizes the necessity of early Cesarean section.

GYNECOLOGY

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Irradiation of Cancer.—Of those who have had a vast experience with the treatment of malignant disease by irradiation therapy, CASE (*Bull. Battle Creek Sanit. and Hosp. Clinic*, 1926, **21**, 54) stands in the front rank, and his opinion in such matters is always worthy of note. Although much has been written on the subject, and we might be led to believe that this form of treatment is fairly well standardized, he states that there is one point which demands serious consideration. Shall the radiation therapy be administered over a longer period of time, with frequent or long intervals between applications, or shall it be given as an intensive therapeutic effort; and, if the latter, shall it be given in the shortest time possible, so that the total irradiation in a case is administered within three or four days or less, or shall it be divided into smaller daily doses and the duration of the treatment protracted to ten or twelve days? The first-named method is pernicious and should be abandoned. By all theoretical and clinical grounds it is shown to be wanting. A definite radioresistance is developed in the diseased tissues, and at the same time the normal cells become increasingly sensitive, so that ultimately the treatment becomes ineffectual. The other two suggestions both really constitute intensive irradiation—in the one case given "brutally," as the French describe it, and in the other given gently, but as a protracted intensive radiation. At one time lively hope was entertained that it would be possible to adhere to a standard "carcinoma dose," "sarcoma dose," and so forth. As a basis for general guidance, it is important to familiarize one's self with the work of the various leaders who have standardized these carcinoma and sarcoma doses; yet, as we are all perfectly aware, it is actually impossible to settle upon a standard physical dosage which will apply to all types of tumor. It is a regrettable fact that the various types of carcinoma tissue offer very great differences in susceptibility to radiation, and this alone makes it important to insist upon a biopsy diagnosis in order to recognize the type of tumor under treatment. It is not enough to say that this or that case is carcinoma, and be content with the carcinoma dose; we must know the classification of carcinoma in order to decide as to its probable resistance or susceptibility to radiation. The physical limitations are obviously those governing the delivery of a sufficient amount of radiation throughout the cancerous tissues. These limitations depend primarily upon the accessibility and anatomic distribution of the lesion under fire, the great variability of cancer cells in their reaction to irradiation, and the extreme sensitiveness of the surrounding normal tissues. There is an additional general sensitiveness of some patients to radiation. All cachectic per-

sons bear roentgenotherapy poorly, but in addition there are some patients who tolerate it poorly even though they have not developed cachexia. As already hinted, certain biologic characteristics of the cancers limit the usefulness of the radiation method; for some tumors, even of the same morphologic characteristics as others which prove very susceptible to radiation, manifest a marked resistance. Tissues which have been subjected to previous radiation are much more resistant, and this argues for the administration of the total dose planned in any case within from ten days to a fortnight. Preoperative treatment is a topic concerning which there is considerable difference of opinion. The author believes in preoperative treatment. The patient is in a better state of health to stand massive dosage than would be the case after operation. Unquestionably the surgeon runs less risk of spreading active cancer cells by the surgical trauma he has to carry out provided anteoperative radiation has been given. In the light of our experimental knowledge that roentgenotherapy will cause atrophy with partial obliteration of the lymphatic channels, coupled with a deleterious action upon tumor cells, the author cannot do otherwise than accept the conclusion that every case of known malignancy should first be submitted to a thorough intensive preoperative exposure of radiation. It is his custom to give the preoperative treatment either three or four weeks before the operation or within two days of the operation. The postoperative treatment is given just as soon as the patient is out of bed, unless the preoperative dose shows an untoward reaction.

A Study of Menstruation.—The work that has been done by LUDLUM and MCDONALD (*Surg., Gynec. and Obst.*, 1925, **41**, 569) is based on the assumption that the smooth muscle of the bismuth laden stomach and intestines as viewed through the fluoroscope and recorded by roentgenographs is a sensitive and mobile mechanism which readily registers the action and condition of the vegetative part of the human organism and is a manifestation of the action of the vegetative or autonomic nervous system, the vagus and the sympathetic nerve apparatus. The vagus and its branches stimulate the muscles and motor mechanism of the stomach to action and inhibit the sphincters. The sympathetic and its branches inhibit the smooth muscles of the stomach and intestines and stimulate the sphincters. Here in the delicate reactions of this large expanse of smooth muscle, as viewed by the Roentgen ray after a barium-sulphate meal, is the best opportunity to record the condition of the vegetative part of the human organism and the condition of the autonomic nerve supply in the movements and arrangement of the smooth or nonstriated muscle of the digestive tract. They have called these manifestations and phenomena the *smooth muscle reaction*. In the course of a much larger study of many and varied conditions they have found that definite alterations in the haustra and arrangement of the intestines occurs as a result of vagus or sympathetic action or the preponderance of one or the other, and a great number of examinations have been made to prove that these effects were constant under similar conditions of colloid and mineral metabolism, and that they were not the result of mechanical filling of the intestine or other accidental

circumstances. They have made experiments to prove that this alteration in the intestinal arrangement is the result of nerve action. As a result of their studies, they conclude that menstruation is a time of vagotonia or vagus stimulation, and that this can be shown in the smooth muscle reaction of the intestine as pictured by the Roentgen ray. The wave of vagus preponderance begins from eight to two days before menstruation, reaches its height during menstruation and returns to the intermenstrual condition from three to six days after menstruation. There is some evidence that this vagus preponderance is partly due to the accumulation of calcium in the blood and tissues, and that calcium is cast off at the time of menstruation. It is possible that some of the preliminary pains of menstruation are due to intestinal cramps from vagus stimulation. Drugs which reduce the vagus stimulation relieve the menstrual pain.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Heterochromia.—HAESSLER (*Arch. Ophth.*, 1925, **54**, 304) summarizes the results of his studies upon heterochromia. Heterochromia exists as an entity characterized by a pale iris in one eye, complicated in many cases by precipitates and cataract. The light color of the iris results from a failure of chromatophores to develop and not from atrophy of chromatophores already in existence. The complications are not the cause of the disappearance of the chromatophores; hence the usual etiologic agents of iritis, such as syphilis and tuberculosis, are not the cause of the color difference of the irides. The prognosis is good. Inflammatory manifestations never become severe and the cataract can be extracted without difficulty. The etiologic agent is unknown, but it must become active very early in life and probably in the embryo. It is probable that a second group of cases exists in which the difference of iris color is associated with unilateral sympathetic hypotone. These cases remain free from precipitates and cataract.

Syphilis Overlooked in Ophthalmology.—RASQUIN (*Rev. gen. d'opht.*, 1925, **39**, 266) presents statistics showing that syphilis recognizable by ocular signs is overlooked in 57 per cent in men and 87 per cent in women. The author believes that this high percentage is due to the fact that the symptoms which reveal the presence of syphilis may pass unperceived in many cases, but more especially because the ocular manifestations, being mostly of a nervous type, appear most frequently where the symptoms of secondary syphilis have been so

slightly marked as to have passed unnoticed. The author infers from these facts the importance of searching systematically for the symptoms of ocular syphilis, treatment of which at a favorable moment may prevent the outbreak of manifestations which are usually grave.

Glaucoma in Myopic Eyes.—KNAPP (*Arch. Ophth.*, 1926, **55**, 35) records 32 cases of glaucoma in myopic eyes; the degree of the myopia was below 5 D. in 26; in 6 it was between 5 and 10 D. The age was over sixty years in the majority; the type of the disease was always the chronic one; the intraocular tension was usually but slightly elevated; in 4 it was low. The cup was shallow and the fields presented the usual defects. As to treatment, some were controlled by miotics, others were operated upon by iridectomy, cyclodialysis or some form of scleral resection; the operation gave, upon the whole, surprisingly good results.

Optic Neuritis and Papillary Stasis. BOSHI (*Ann. d'ocul.*, 1925, **162**. 624) emphasizes, in disease of the optic papilla, the importance of taking into account the affection which provokes involvement of the nerve. A favorable outcome leading to complete disappearance of all ophthalmoscopic signs is frequent in stasis; it is exceptional in optic neuritis. The differential diagnosis is frequently difficult between these two forms, and that the more so as mixed cases occur, so that some ophthalmologists decline to make a distinction and prefer to speak of optic neuritis in both forms. But the evolution of the ophthalmoscopic signs compel us to consider them as distinct disease forms, distinguishable as stasis which is susceptible of perfect cure, and optic neuritis which is so frequently followed by atrophy.

Brain Tumors.—BOSTROEM (*München. med. Wchnschr.*, 1925, **72**, 331) analyzes 72 cases of brain tumor in the wider sense of the term, including all space-filling processes within the cranium. The diagnosis was confirmed in 40 cases by operation or section; in 2 cases the diagnosis was not made, and wrong in 1; in 5 the side of the lesion was correctly determined, but further localization was impossible; in 4 localization was only probable, but 3 of these were proven correct; in 1 localization, including the side upon which the growth was situated, was impossible; thus in 27 cases the clinical diagnosis was proven correct. Neurologic methods alone were employed, aëration of the ventricles not being practised. The author regards the results of operation as, upon the whole, unsatisfactory; he ascribes this partially at least, to the fact that the diagnosis of brain tumor is so frequently made too late. He recapitulates the early symptoms, such as headache, but observes that this symptom is by no means always present in the beginning; the same is true of visual disturbances (choked disk and hemianopsia), convulsions, psychic aberrations, etc. The importance of ophthalmoscopic examination is emphasized, as also the Roentgen rays and monolateral deafness. Tumors of the frontal region, when they are at all capable of diagnosis, are apt to be quite large when first recognized, so that operation should not be delayed in these cases. Early diagnosis appears attainable; perfection of surgical technique will do the rest.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Nasal Sensitization, Nasal Anaphylactic Shock and Respiratory Symptoms Simulating Bronchial Asthma, in the Guinea Pig.—Having shown that horse dander is anaphylactogenic and that there is a definite crossed anaphylactic relationship between horse dander and horse serum, RATNER, JACKSON and GRUEHL (*Proc. Soc. Exper. Biol. and Med.*, 1925, **23**, 16) employed the guinea pig as the experimental animal to study the mechanism of an idea previously conceived by Ratner, that is, that in children asthma may be an "acquired" disease, and in some cases the result of sensitization through the nasal route. It was found that those guinea pigs which were sensitized by exposing them to the dust of dried horse dander died after subsequent intravenous injection of a protein extract of this same horse dander. Animals sensitized by giving them intraperitoneal injections of horse dander extract later showed grave anaphylactic phenomena and, also acute death when exposed to horse dander dust. Those guinea pigs which were sensitized by exposing them to horse dander subsequently exhibited marked respiratory anaphylactic phenomena when subjected to the same horse dander dust. This latter group of animals, which at no time had received parenteral injections of the protein extract of horse dander, presented symptoms which were comparable to the bronchial asthma of human beings. The guinea pigs came into contact with the horse dander in the same manner that a human being might, for at no time was the horse dander forcibly injected into their nares. Feeding dry horse dander in gelatine capsules failed to sensitize the animals. The authors believe that their experiments "lend evidence for the probable mechanism of bronchial asthma in the human being, and further demonstrated that the nasal route may be an avenue for the production of sensitization, anaphylactic phenomena and even anaphylactic death."

The Pathogenesis of Polyposis Nasi.—"The conception of the pathogenesis of the nasal polyp, in the minds of the majority of rhinologists and even pathologists, is hazy. Billroth was the first to enunciate the theory that the nasal polyp was nothing more than the normal mucous membrane of the nose, which, when stimulated by some irritant or trauma, becomes edematous." The second great step forward in the development of the true pathogenesis of the nasal polyp we owe to Zuckerkandl who was the first to demonstrate that the mucous membrane about the ostia of the accessory sinuses and its extension into these cavities is particularly thin, and the underlying connective tissue stroma is exceedingly delicate and loose, so that it reacts to trauma or irritation by becoming edematous. Hajek contributed a third basic factor to the proper understanding of the pathology of nasal polypi by

pointing out that the loose alveolar tissue of the mucoperiosteal layer of the normal accessory sinuses is in close connection with the hollow marrow and spaces of the underlying bone. The fourth phase of this problem, that the nasal polyp is a gross ocular manifestation of an underlying chronic osteomyelitis of one or more of the paranasal sinuses, has been elaborated by FREEDMAN (*Arch. Otolaryngol.*, 1925, **2**, 250). His attention was directed to these observations in studying a polyp removed from a women, aged forty-five years, who had suffered from nasal obstruction and purulent rhinitis for two years. He was able to say from his studies that the nasal polyp is a localized edema and prolapse of the normal mucous membrane of the nose and that the edema may be caused by an infection or by trauma. He believes that the great majority, if not all, of nasal polypi are in the vicinity of, or protrude through, the ostia of the accessory sinuses. Because of this situation about the sharp margin of the ostium, gravity causes a compression of the returning vein, occasioning a further edema of the body of the polyp. A "full blown" polyp, when not due to postoperative trauma, is always a symptom of bone involvement of one or more of the accessory sinuses of the nose. As free drainage and ventilation of the involved sinus is consequently prevented, a stagnation results with an extension of the infection into the deeper structures causing a periostitis, ostitis and finally an osteomyelitis, which occurs quite easily in the ethmoidal labyrinth due to the fact that the marrow spaces communicate directly with the loose alveolar mucoperiosteal stroma. The author emphasizes the fact that a nasal polyp is only a symptom of an underlying osteomyelitis, at least a periostitis, depending on the sinus involved. Consequently it is imperative that any operative prosedure in these conditions must be directed at the basic processes and chould not be limited to the removal of the polyp or polypi.

RADIOLOGY

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The Use of Corpus Luteum to Prevent Nausea in Radiation Therapy of Uterine Conditions.—Finding radiation sickness a very annoying problem in radiation therapy, LAFFERTY and PHILLIP (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 449) have found that in uterine conditions, if corpus luteum is administered intravenously immediately after treatment in 1 to 2 cc. doses that there is a marked lessening of the so-called radiation sickness. In 16 cases so treated, 10 were entirely relieved, 4 improved and only 2 unimproved. These 16 patients were known to

have marked nausea following treatment, but with the administration of corpus luteum they responded as stated above. The authors feel that these results warrant further investigation of this method of treatment.

The Effect of Effort on the Size of the Heart.—GORDON (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 424) reports on a study of animals and Marathon runners of the effect of effort on heart size. He found that rabbits that were run to exhaustion in the treadmill, both those with normal hearts and those with chronic myocarditis, showed a definite diminution of heart size immediately following effort, amounting to an average of 19 per cent. The recovery was prompt and without residual bad effects. Again, observations were made on Marathon runners, immediately after a race, and he found that the heart was small, and during the day following the race there was a gradual return to normal size. In a series of plates taken over a long training period he was unable to find any evidence of cardiac hypertrophy or dilatation. The author draws the conclusion, therefore, that exercise does not cause cardiac dilatation and that prolonged athletic training does not develop hypertrophy of the heart.

The Diagnosis and Treatment of Intrathoracic Lymphadenopathy from a Roentgenological Viewpoint.—In a preliminary report on his investigations in the treatment of intrathoracic adenopathies by Roentgen ray, LAWSON (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 427) calls attention to the fact that tuberculous adenopathy accounts for about 80 per cent of the intrathoracic glandular enlargements. The next in frequency are the adenopathies due to the acute infectious diseases of the chest. The history is important in the diagnosis of hilus adenopathy, and usually contains the more common symptoms of chest tuberculosis. The d'Espine sign is one of the most important of the physical findings, and the spinalgia of Petruschky is present in 50 per cent of the cases. The roentgenologist and the internist must work in close coöperation to properly recognize this condition. The author states that in cases of hilus adenopathy, barring those of acute infections, there can generally, if not always, be found evidence of a primary pulmonary focus. He has treated these adenopathies with the Roentgen ray and has had very prompt and definite recession of the hilus shadows to normal, this treatment being in conjunction with the regular medical and hygienic treatment. Lawson has found that best results come from a judicial use of short or long waves as each case may require, giving repeated doses rather than massive doses. Treatments are given at six weeks' intervals. Thus far this investigation has been in progress for less than a year, and therefore the author holds that the technic is still in the experimental stage and cannot be more definitely standardized in this preliminary report.

Roentgen Ray Treatment of the Bowen Type of Skin Cancer.—HAZEN (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 450) reports 9 cases of the Bowen type of skin cancer which he has treated by the Roentgen ray, obtaining very satisfactory results. The lesions are usually multiple, and roughly can be divided into large and small plaques, nodules,

fungating tumors and keratoses. These may coexist and grow very slowly. Histologically these plaques are cancerous, and the malignant cells arise from the basal cells of the rete. Of fifty-eight lesions in these 9 cases, thirty-eight were readily cured, eight large plaques and seven small plaques were cured with difficulty, and two small plaques and three keratoses were resistant.

The Diseased Appendix as a Cause of Acidosis in Children.—The opinion of the late McGuire Newton that the non-acute pathological appendix is often the cause of a variety of disturbances in children is supported by GRAY (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 436) in a series of cases which he has studied roentgenologically. He has made his diagnosis of diseased appendix upon the following signs: (1) Abnormalities in the lumen; (2) marked delay in emptying after the contents of the cecum have been expelled; (3) abnormal fixing or fixed kinking; (4) the presence of retained fecal concretions, and (5) tenderness in the appendix. The presence of indirect evidence, as pylorospasm, ileal stasis, or colonic spasticity, aids the diagnosis. In these cases after removal of the appendix the patient was relieved of the troublesome symptoms which previously had not yielded to other types of treatment.

Roentgen Findings in the Uncommon Causes of Hemoptysis.—Among the uncommon causes of hemoptysis, BEILIN (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 304) says that lung abscess, neoplasm, bronchiectasis, foreign bodies, chronic bronchitis with asthma, pneumoconiosis, chronic infections due to actinomycosis, blastomycosis, streptothricosis, pneumonia, syphilis, acute lymphatic leukemia and other unspecified causes are found. The ray will early reveal a pulmonary lesion and its probable nature. Six case reports are cited to illustrate this, with a discussion of roentgenologic differential diagnosis.

Report of 5000 Gastro-intestinal Examinations by the Roentgen Ray.—MERRILL (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 310) presents this report as a result of routine examinations made in a busy clinic. Fluoroscopy is preferred to the serial plate method for various reasons, especially economy and saving of time. Observations can be made from palpation and visualization, the latter at least as well as from the plate. The proven error in 818 cases was 4 per cent. No gastric ulcer or carcinoma found at exploration was missed by the Roentgen ray. Two duodenal ulcers were missed. In 551 cases of ptosis by the Roentgen ray, ulcer had been diagnosed clinically, or in 28 per cent. In duodenal ulcer only half were diagnosed clinically, and approximately the same in gastric ulcer. Of 97 cancers found at operation, 95 were so diagnosed by the Roentgen ray.

Roentgen Ray Therapy in Bronchial Asthma.—RAMIREZ and COLE (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 322) quote 35 case reports. Twenty-five were negative; 5 were temporarily improved; 5 continued to improve for six months or longer. Comment is to the effect that present technic perhaps needs modification, or a more careful selection of suitable cases might yield more encouraging results.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Mental Disease in the United States in Relation to Environment, Sex and Age, 1922.—POLLOCK (*Am. J. Psychiat.*, 1925, **82**, 219) presents graphs for each of the major psychotic groups constituting first admissions (63,624) for about all mental hospitals in the United States for the year 1922. Cities and villages with a population of 2500 or over are called urban. Below this population everything is classified as rural. The urban populations contribute much more than half of all the first admissions. In special groups such as general paresis, alcoholic psychoses, and psychoneuroses the males, regardless of habitat, outnumbered the females having these diseases. On the contrary, females, regardless of habitat, formed a majority of the manic-depressive or involution melancholia groups. The author feels that city life is too complex for the equipment of many people and hence preventive psychiatry will have to face the analysis of the problem of making persons more stable and cities less complex. He thinks syphilis and alcoholism can be eradicated.

Lumbar Puncture Headaches.—ALPERS (*Arch. Neurol. and Psychiat.*, 1925, **14**, 806) reviews the literature and cites his experience with 91 lumbar punctures, in which 16 developed headaches. The headaches did not seem to correlate with the quantity of fluid withdrawn. Headaches seemed to occur in patients in whom the pressure was reduced most when the fluid was withdrawn. In many of these it went to zero. Pituitary extract (1 cc.) given intramuscularly relieved 14 of the 16 patients with headache. Hypotonic salt solution (100 cc. of 0.5 per cent) given intravenously relieved the two severe cases within three hours. He advocates the use of a small needle.

The Conditioned Reflexes and Children's Neuroses.—KRASNOGORSKI (*Am. J. Dis. Child.*, 1925, **30**, 763), following the work of Pavlov, performed experiments on children in which conditioned reflexes were produced. By using stimuli nearly like the one to which the reflex was conditioned the children were observed to become very irritable and the latent period of the reflex became longer. Sleep itself was induced as a conditioned reflex in some other experiments. Sleep resulted frequently in the attempt to delay reflexes and the delaying of reflexes caused them to disappear. They were renewed only with much repetition. A girl, aged twelve years, with globus hystericus and frequent vomiting attacks was studied. The conclusion was that she over-

reacted to irritation at one time and over-inhibited at another. The conclusion is that in such a child the normal balancing relations between irritation and inhibition are markedly disturbed and that conditioned reflexes are both very difficult to establish and to remove. The author thinks this is the basis for the psychopathology in her case. A boy, aged six years, who had had epidemic encephalitis two years before, was studied. He had attacks of excitement with destructiveness, dyspnea, intensive salivation. He had insomnia and his behavior was worst when resisted. The conditioned reflexes were formed sooner in this boy than in normal children. The inhibitory processes were very deficient. When an attempt was made to induce sleep by repeated conditioned inhibitions, he became excited. The author believes that neuroses develop in children in the conflict between irritation and inhibition. Bromides are thought to intensify the irritation as well as the inhibition and are therefore thought to be a good cerebral regulator in functional cases. Rest and analysis of conflicting reflexes are mentioned as other forms of treatment for such cases.

Pleasure and Deterioration from Narcotic Addiction.—According to KOLB (*Ment. Hyg.*, 1925, **9**, 699) the pleasure derived from the relief of pain or anxiety by opiates is negative pleasure. The pleasure which such drugs induce in the emotionally unstable psychopaths or neurotics in elevating them to a new level of feeling is positive pleasure. Few normal persons ever experience the positive pleasure which is likened to elation, a thrill, a very pleasurable sensation approaching ecstasy. The psychopath in order to escape the conflicts, tensions, and boredom of his inadequacy takes his first dose and gets positive pleasure. Immediately afterward he sinks into a depression from which he tries thereafter to boost himself with opiates. He rarely experiences positive pleasure after the onset, but in his endeavor to attain that good and escape depression, takes increasingly larger doses and thus develops a tolerance. Cocaine is stimulating to all types of people. It gives a sense of physical and mental power. Excessive doses produce marked anxiety and apprehension. It is often taken to counterbalance the effect of alcohol or opiates. Case histories are cited which illustrate the unusual pleasure derived from the use of cocaine with opiates. Cocaine is more deleterious in its effects than opium. Deterioration from opiates is due to the physiological effects of the drug and the social consequences. The greatest amount of deterioration from opium is produced in the carefree mildly neurotic persons with a slight personality bias. Being unstable, such persons nevertheless stand a chance of succeeding in the world. Normal persons have been addicted for years without change in their moral or intellectual make-up. The psychopathic group have little to lose with or without drugs. What in the past has been interpreted as deterioration among psychopaths due to use of drugs was an "original nervous instability and moral obliquity." Many excellent case histories are given to illustrate the many types of addiction. About half of the addicts studied had a poor industrial history. Thirty-nine per cent of the married addicts were separated or divorced. Sexual potency was present in addicts of years' standing. Large doses (15 to 30 grs. of heroin) must be taken daily to abolish sexual potency. Heroin apparently is no more deteriorating in its effects than morphine.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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The Relation between the Reducing Powers of Bacteria and Their Capacity for Forming Peroxid.—In this paper M'LEOD and GORDON (*Jour. Path. and Bacteriol.*, 1925, **28**, 155) investigate the relationship between this H_2O_2 production and the reducing power of the bacteria. The present state of knowledge concerning the reducing power of bacteria is reviewed. The experimental work relates more particularly to the thermostable substances present in animal tissues and yeast, which give a nitroprussid reaction in the reduced state. It had previously been shown by another worker that this reaction was chiefly due to glutathione. It was presumed that this was produced from the medium by reduction. One result of the work was a classification of bacteria as follows: (1) Strong reducers—the anaërobes, paratyphosus B and Vibrio choleræ; (2) moderate reducers—certain coliform bacteria; (3) nondoubtful or doubtful reducers—staphylococcus, meningococcus and a number of others. Another line of investigation was the power of different bacteria to bring undissolved cystin into solution. The same grouping was again suggested. A third phenomenon, that of green-ring production in heated blood agar, gave a similar grouping of the bacteria. The relationship of reduction of glutathione to reduction of various dyes and the heat resistance of the bacterial reducing mechanism was studied. The conclusions were reached that the necessary consequence of bringing a reducing mechanism into contact with oxygen is the production of H_2O_2; that all bacteria have reducing properties but these vary greatly from species to species; that the reducing bacteria are H_2O_2 producers; that the amount of H_2O_2 produced would necessarily be limited by the sensitiveness of the bacteria to that substance and that the bacteria generate active hydrogen.

The Significance of Bacterial Allergy as a Sign of Resistance.—The thought that allergic hypersusceptibility might indicate increased resistance is an obvious deduction from the earlier superinfection experiments of Koch. The extremely rigid controls used by ZINSSER, WARD and JENNINGS (*Jour. Immunol.*, 1925, **10**, 719) in their experiments give added weight to the evidence that allergy does indicate an increased specific adjustment of the tissues for response to the stimulus of infection, and a consequently enhanced capacity for the rapid mobilization of a protective mechanism. The experiments consisted of a series of guinea-pig injections, including controls. A number of animals were treated with the Dreyer de-fatted tubercle bacillus material and a number with tubercle bacilli killed by heating to 80° C.

for one and a half hours. The protection and the allergic reaction (skin tuberculin test) was lower in the Dreyer-treated animals than in those receiving dead whole bacteria, and both these series showed a quite consistent prolongation of life as compared with the controls. The authors believe, if their conception of the mechanism involved is a correct one, that the artificial production of allergy by dead bacilli or other products appears a hopeful direction for the investigation of immunization in tuberculosis.

Primary Lung Tumors in Mice following the Cutaneous Application of Coal Tar.—As it is not unusual for mice to develop pulmonary tumors, MURPHY and STURM (*J. Exper. Med.*, 1925, **42**, 693) carried out some experiments on mice which showed that the external application of tar, even though done in such a fashion as to cause no skin lesion, will, if done sufficiently long, result in a 60 to 78 per cent incidence of lung tumors. Control mice from some stock kept three to six months longer, and for that reason more liable to spontaneous tumors, failed to show a single instance of such growths. These tumors were identical with primary tumors of lung in mice previously described by Livingood, Haaland and others. They were adenocarcinomatous, papillary cystadenomatous and adenomatous in character. The mechanism of the tar action is not clear. The authors tend to support the hypothesis that a reduction of the animal's resistance to cell growth is brought about by the tar applications and then chronic irritation of the lung by inhaled dust may bring about the lung tumors.

Leukemia, Pseudoleukemia and Related Conditions in the Slye Stock of Mice.—SIMONDS (*J. Cancer Res.*, 1925, **9**, 329) reports that in the first 15,000 necropsies of the Slye stock of mice 316 showed enlargements of the lymph glands and spleen. Out of these 316 there were 67 leukemias, of which 28 were of the lymphatic and 39 of the myelogenous type; 111 pseudoleukemias; 51 lymphosarcomas. The remainder was divided into lymphomas; lymphoid hyperplasias associated with infection; Hodgkin's disease. Typical instances of these conditions can be recognized without great difficulty. Leukemia and pseudoleukemia show marked invasive power of the cells of the lymphoid tissues, the cells growing through the walls of veins and the capsules of lymph glands and infiltrating the surrounding tissues. In both there is a widespread involvement of the lymph glands of the body with infiltration of one or more of the viscera without relation to the glands. They differ from each other in the number of nucleated cells in the blood. Lymphosarcoma is distinguished by its greater invasiveness and by being localized in one group of glands from which it may invade related organs. Generalized lymphosarcomatosis does occur in which the manner of spread is not readily apparent. Borderline or transition cases were found to be very numerous, and the author suggests that they are probably fundamentally of the same nature and probably belong among the true neoplasms. Lymphoid hyperplasia may be either local or generalized, and differs from the above-mentioned conditions chiefly in the absence of the quality of invasiveness.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF
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Viability of Bacillus Typhosus in Stored Shell Oysters.—KINYOUN (*Pub. Health Rpts.*, 1925, **40**, 819) reviews previous work on the subject and reports his own experiments which showed that oysters were aroused from hibernation, fed with Bacillus typhosus and then stored. Bacillus typhosus was being recovered fifteen days after the oysters had been fed with the organism, when the tests were discontinued.

Results Obtained with the Dick Test Before and After Immunization with the Toxin of the Hemolytic Streptococcus of Scarlet Fever.—DYER (*Pub. Health Rpts.*, 1925, **40**, 593) shows that among a group ol 328 boys of an average age of 16.8 years in an institution 17.1 per cent were found to give a positive reaction by the Dick test, indicating susceptibility to scarlet fever. The susceptibles were immunized with scarlet fever toxin, The large majority, when retested, showed negative reactions. There was no noteworthy difference between those receiving toxin with a preservative and those receiving toxin without preservative.

Effect of Repeated Injections of Avirulent Diphtheria Bacilli, Bacillus Hofmanni and Bacillus Xerosis in Guinea Pigs—ROSENAU and BAILEY (*J. Infect. Dis.*, 1925, **37**, 97) state that the object of their experiments was to determine whether avirulent diphtheria bacilli are able to stimulate antitoxin production and thus account for the acquired immunity to diphtheria which most persons develop with maturity. Seventeen different strains of avirulent cultures and also cultures of related organisms, such as Bacillus hofmanni and Bacillus xerosis, were injected into guinea pigs over a long period of time. The Schick test remained positive for all these guinea pigs, and when the final test was made they showed no immunity to diphtheria toxin. It was found that there is considerable individual variation in guinea pigs so far as their response to injections of diphtheria toxin is concerned. Usually the Schick test becomes negative for guinea pigs in three months, and they then are immune. The Schick test in one animal remained positive after thirty-nine injections of small doses of diphtheria toxin ($\frac{1}{125}$ to $\frac{1}{8}$, minimum lethal dose) over a period of fifteen months. This guinea pig received a total of 1.94 minimum lethal dose. If such experiments, with avirulent cultures, could be continued over a series of years, it is possible that some immunizing effects might be manifest. The studies

emphasize the essential difference between the socalled avirulent diphtheria bacilli and the true Klebs-Löffler organism. Not only did the avirulent strains fail to induce immunity, but their agglutination reactions showed that there is a wide immunologic gap separating them from the diphtheria bacillus. Some of these socalled avirulent strains have pathogenic properties. They found that a few of our guinea pigs that received repeated massive injections of live cultures developed disseminated focal lesions, which are being studied. No change in virulence was observed in cultures of avirulent diphtheria bacilli or Bacillus hofmanni or Bacillus xerosis under observation for eighteen months, and transferred for thirty-six generations on Löffler's blood serum. Guinea pigs react with striking uniformity to the Schick test. All guinea pigs appear to be like some children in that they are persistently positive. The guinea pig's skin seems to be more sensitive than the human skin, for a typical reaction is produced by the intradermal injection of $\frac{1}{250}$ minimum lethal dose. Pregnancy and general systemic infections appear to inhibit the local skin reaction. Pseudoreactions were not observed in the studies as a result of the injection of diphtheria toxin; but sensitized guinea pigs responded to the injection of bacterial antigens, although this reaction is not specific. With certain bacterial extracts containing bacterial protein a local necrotic action of the skin was produced which was interpreted as a modified Arthus phenomenon. Experimental confirmation was obtained of the correlation between a positive Schick test and susceptibility and a negative Schick test and immunity. In a series of guinea pigs it was furthermore found that a definite relation exists between the weight of the animal and the minimum lethal dose of diphtheria toxin. It takes about twice as much diphtheria toxin to kill a guinea pig, weighing four times as much as the standard control; in other words, if the minimum lethal dose for a 250-gm. guinea pig is 0.011 it will take 0.022 for a guinea pig weighing 1000 gm. Morphologically the avirulent diphtheria bacillus resembles the true Klebs-Löffler organism, but the results recorded above emphasize the fundamental difference between the two groups, and throw doubt on the appropriateness of the name "avirulent diphtheria bacilli."

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 15, 1926

A Rapid Method for the Preparation of Crystalline Isoelectric Hemoglobin by the Electrodialysis of Red Blood Cells.—W. C. STADIE and E. C. Ross (from the Department of Research Medicine, University of Pennsylvania Medical School). The methods extant for the crystal-

lization of hemoglobin depend upon lowering the solubility of hemoglobin in its watery menstruum, either: (1) By changing the menstruum from water to water alcohol or water ether; or (2) by lowering the temperature to about 0° C., simultaneously favoring the formation of relatively insoluble isoelectric oxyhemoglobin by treatment with a CO_2-O_2 mixture. The crystals obtained are finally freed of electrolytes by dialysis in collodion or parchment sacs. The first method is open to the serious objection that alcohol or ether may and often does produce changes in hemoglobin (that is, diminution of its oxygen-binding properties), making it unfit for many physicochemical studies. The second method, described by Heidelberger (1923), overcomes this objection in part but not entirely. On the average, our samples of hemoglobin from horse blood by this method contain 10 to 15 per cent of the inactive form. Both these types of methods are laborious and require at least one week for the preparation of the crystalline product. The method given in this paper overcomes in large measure these two undesirable factors. By the electrodialysis of washed red cells in an easily constructed apparatus, the following advantages have been secured: (1) All procedures are carried out at room temperature. (2) No foreign substance is added to the blood. (3) The short time necessary for the entire procedure (about three to five hours) eliminates practically completely the formation of "inactive" hemoglobin. (4) Hemolyzing agents are not needed; hence, the only preparation of the cells necessary is adequate washing with saline. (5) A large proportion of the inorganic ions, including base bound with hemoglobin, is rapidly (two to three hours) dialyzed out of the hemoglobin solution; in consequence, isoelectric oxyhemoglobin, which is relatively insoluble in water, crystallizes out at room temperature. (6) The yield is about 65 per cent of the hemoglobin originally present in the cells. The description of the apparatus is as follows: Two half boxes made of stout ($\frac{3}{4}$ inch) boards and two sheets of dialyzing parchment are fitted together with the proper interposition of rubber gaskets and held firmly by four long bolts and wing nuts. This gives an apparatus with three separate water-tight compartments—two side electrode compartment made of the two half boxes and a center compartment made of dialyzing parchment. Since considerable heat is developed during the passage of the current, a vigorous stream of water is kept running through each electrode compartment. The electrodes are of sheet brass or copper about $\frac{1}{32}$ inch thick, and are fitted into slots $\frac{1}{2}$ inch from the parchment on either side. A series of holes in the electrodes allow for the drainage of the water. The electrodes are connected with the terminals of a 110-volt direct current. The technique of hemoglobin crystallization is: Two hundred cubic centimeters of well-packed, washed horse or dog cells are poured into the center compartment. A vigorous stream of tap water is allowed to run through the apparatus and the current (110-volt direct current) turned on. After three to four hours there is an abundant crystal formation. By means of suction the crystals and mother liquor are transferred to a 250-cc. centrifuge tube. A considerable amount of crystals adheres to the anode parchment which should be scraped after removal from the box and the crystals transferred to the centrifuge tube which is centrifuged for about thirty minutes. The supernatant liquor is poured off and

the top surface of the packed crystals is washed once without mixing with ice-cold distilled water. The yield is 50 to 75 per cent. The analysis of the crystals is as follows: Analysis of the crystals shows the following average composition. Hemoglobin, 40 per cent by weight; H_2O, 60 per cent; base, 0.02 mole per mole of hemoglobin; no chlorids, sulphates, phosphates or carbonates. Oxygen capacity is 98 to 100 per cent of total pigment present.

Normal and Compensatory Growth of the Kidney (Albino Rat).—M. ARATAKI (from the Wistar Institute of Anatomy and Biology, Philadelphia). During normal growth, from birth to old age, the number of fully formed glomeruli in one kidney increases from 10,700 at birth to about 30,500 at one hundred days. From this age to three hundred and fifty days the number varies only slightly, but by five hundred days it has dropped to about 20,000. The equivalent ages for man are: Eight years equals one hundred days; thirty years equals three hundred and fifty days; forty-two years equals five hundred days. While the glomeruli are increasing in number they are also increasing in diameter, and the same is true for the convoluted tubules. In both cases the rapid increase in diameter occurs during the first one hundred days, and for the glomeruli is greatest at five hundred days, when, however, the number of glomeruli is much diminished. This relation is still to be explained. In compensatory growth the surviving kidney increases in weight at eighty days, 63 per cent females and 80 per cent males, after unilateral nephrectomy, and somewhat less after unilateral hydronephrosis. There is no increase in the number of glomeruli above the normal in either case of compensatory growth. The growth depends on the enlargement of the glomerular unit system. This enlargement is in the same ratio as that of the entire kidney, and is harmonious as between the glomeruli and their associated tubules. When comparison is made with the human kidney it appears that it has the same proportion of glomerular substance as is found in the corresponding rat kidney. Conclusion: Normal growth of the kidney is characterized by an increase in the number of the glomerular unit systems—accompanied by enlargement. In compensatory growth there is no increase in these systems above the normal, but enlargement is attained by their hypertrophy, which is harmonious as between the glomeruli and tubules. (Arataki, M.: Am. J. Anat., 1926, **36**, 399.)

Some Factors in the Production of Capillary Stasis by Concentration.—E. M. LANDIS (from the Department of Physiology, University of Pennsylvania). Krogh (*The Anatomy and Physiology of Capillaries*, Yale University Press, 1922) has described a method of identifying the passage of fluid through the capillary wall with the production of stasis due to concentration of the blood. This is particularly evident after the application of urethane in 5 and 25 per cent solution to the tongue or web vessels of the frog. Chiefly on the basis of these experiments, he believed that the rate at which fluid passes from the capillary is determined by the degree of dilatation and is due to an increased permeability of the stretched endothelium. It seems possible, particularly in view of the evidence in favor of Starling's hypothesis of fluid

interchange, that other factors, such as rise of capillary pressure, injury or osmotic effects, might explain this activity of urethane, and should be definitely excluded before the passage of fluid is ascribed to dilatation as the only factor. Experiments to test these alternative factors were carried out on the mesenteric capillaries of the frog. Micropipettes, of 4 to 8 μ diameter at the tip, were inserted directly into the capillaries, and the capillary pressure was measured in the field observed by a method already described by the author (*Am. J. Physiol.*, 1926, **75**, 548). It was found that an increase of capillary pressure to over double its normal value, while producing obvious concentration of the blood after some minutes, was insufficient in itself to cause stasis. Local mechanical injury by the pressure of a microscopic glass rod, however, produced even at low capillary pressure a restricted area of stasis resembling markedly the condition seen after urethane. By direct measurement during the application of urethane it is found that pressure rises in the capillary net from 2 to 6 cm. of water above normal during the period of increased flow. As concentration becomes evident, and the resultant increased viscosity impedes venous outflow, capillary pressure rises, approaching the arteriolar level, with the result that concentration is accelerated. The production of stasis may be stopped if the arteriole is compressed and capillary pressure thereby allowed to fall. Urethane in 5 or 25 per cent solution is markedly hypertonic. Nevertheless the observed outflow of fluid is not to be attributed to an osmotic factor, since it appears that the narcotic rapidly penetrates the endothelium. An isotonic solution of urethane, 1.5 per cent in distilled water, causes a swelling and disappearance of the red cells inside the capillary almost as quickly as distilled water alone. Measurements of capillaries in photomicrographs taken before and after the application of urethane show that dilatation need not necessarily accompany a condition of stasis. Constricted capillaries of 6 to 7 μ diameter have been photographed in typical stasis. Injury to the capillary should be considered, since 25 per cent urethane causes swelling and disintegration of the erythrocytes in the capillaries and of the pigment cells about the larger vessels. Even with the 5 per cent solution stasis is always irreversible. In the rare instances when there is a return of flow after stasis caused by 1.5 per cent urethane in Ringer's solution no diminution of capillary diameter is observed, and the erythrocytes tend to stick to the endothelium, suggesting a toxic action. In view of these results, it appears that dilatation is not the only factor involved in the increased permeability of the capillary observed after the application of urethane.

The Pancreas and the Thyroid Apparatus.—F. S. HAMMETT (from the Wistar Institute of Anatomy and Biology, Philadelphia). The production of a thyroid deficiency (thyroparathyroidectomy) in the male and female albino rat at different ages (twenty-three, thirty, fifty, sixty-five, seventy-five and one hundred days) is followed by a retardation of the growth in weight of the pancreas which increases in degree with the increase in the age of the animal at the time of the initiation of the glandular deficiency. The direction of the change in response of the organ with advancing development is like that shown by the body weight. The same similarity in pancreas and body weight

response is exhibited in conditions of parathyroid deficiency occasioned at progressive ages. Since both thyroid and parathyroid deficiency are productive of a decrease in the amount of material available for growth, it is clear that the growth processes of the pancreas are similar to those of the body as a whole, and hence not uniquely related to thyroid or parathyroid activity as such. The degree of retardation of pancreas growth is greater in the case of thyroid than in the case of parathyroid deficiency. Hence it is clear that the pancreas is more dependent upon the maintenance of a normal metabolic rate (thyroid) than upon the preservation of the nutritional level (parathyroid). This is supported by the fact that the degree of retardation of pancreas growth is practically the same as that of the body as a whole in conditions of parathyroid deficiency, while in conditions of thyroid deficiency the growth of this organ is retarded more than that of the body. This greater sensitivity of the pancreas to the lowered metabolic rate is to be attributed to its inherent high normal functional activity and not to any specific thyroid relationship. Of great significance is the fact that the growth processes of the pancreas in their relation to the metabolic and nutrient levels are strongly conditioned by the factors introduced at puberty—factors which presumably emanate from the activity of the gonads occurring at this time. This is shown by the fact that the growth of the pancreas subsequent to thyroid removal is not only absolutely stopped at the beginning of puberty but is even retrogressive (the organ loses weight) and the fact that a marked increase in the degree of retardation occurs at the same time under conditions of parathyroid deficiency.

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